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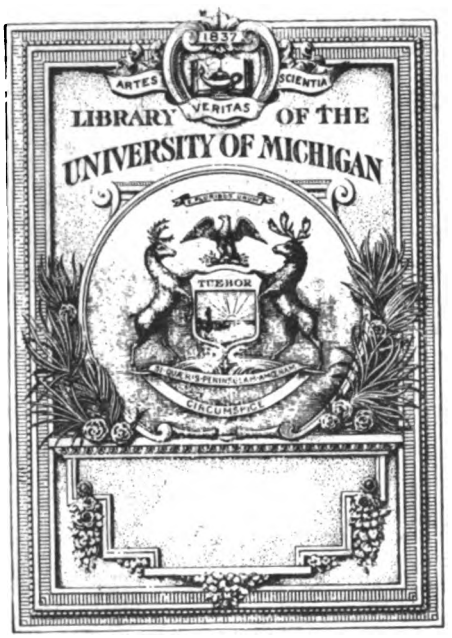

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A STUDY OF A TOXIC SUBSTANCE OF THE PANCREAS.*

By E. W. GOODPASTURE and GEORGE CLARK.

(From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins Medical School.)

The interesting pathology of acute hæmorrhagic pancreatitis has led investigators to search the pancreas for poisonous material, the absorption of which from the necrosed gland might explain the profound intoxication associated with the disease. Researches in this direction have led to the discovery that autolyzing pancreas is toxic. That is to say, if a fresh sterile pancreas of one dog is placed in the peritoneal cavity of another, as the gland autolyzes, the latter animal rapidly manifests symptoms of poisoning comparable to those occurring in spontaneous hæmorrhagic pancreatitis. Two main views are held regarding the nature of the toxic agent. The one identifies it with active trypsin, the other with split-products of proteid resulting from digestion. Lattes has recently shown that trypsinogen is activated by something present in the dead pancreas cells, so that trypsin digestion takes place fairly rapidly in the autolyzing gland. This fact would, of course, support either of the two theories, though Lattes himself inclines toward proteid split-products as the toxic substance.

Our interest was directed to this study while engaged in an investigation with Whipple of the peritoneal exudate in experimental acute hæmorrhagic pancreatitis, which was found to be non-toxic; and as we could discover in the literature no really serious attempt to isolate a toxic agent from the fresh or autolyzed pancreas, it seemed of interest to undertake experiments with the idea of purifying the toxic part of the gland as much as we could, and of studying its physiological effects when more or less isolated from other material. We have used for these experiments the pancreas of the dog, which limited our observations to relatively small quantities of material. Yet it has been possible to show that (a) a toxic constituent is present in the fresh gland before trypsinogen can have been activated; (b) each pancreas contains about one lethal dose for an animal of equal size; (c) the toxic fraction is present in the B-nucleo-proteid, and therefore is thermo-stable; (d) it is gradu-

* Abstract.

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ally destroyed by autolysis, but can be obtained in a concentrated form from a 24-hour autolyzed gland; (e) it is itself a proteid or is in a physical or chemical combination with a proteid; (f) the injection intravenously or intraperitoneally of an intoxicative dose elicits symptoms comparable to those present in acute hæmorrhagic pancreatitis.

Fresh Pancreas Extract.

The gland is removed from a dog under aseptic conditions. It is cut finely and ground with washed sand. Fifty cubic centimeters of .9 per cent NaCl solution in water are added and mixed thoroughly by grinding the macerated gland. The material is then filtered through gauze and cotton. The filtrate injected intravenously into another animal causes a rapid fall in blood pressure with a more gradual, but prompt, return to normal or above, and a delay in blood-coagulation time. In from 1 to 3 hours after the injection symptoms of extreme intoxication appear, persistent vomiting of bile-stained mucus, profuse diarrhœa which becomes bloody, often bleeding from the gums, profound fall in the blood-pressure, in the leucocytes, and in body temperature, slow deep respiration, a weak rapid heart, rigidity of the abdomen, and finally coma and death, if the dose be sufficient. If the dose be not lethal, the animal gradually recovers, the temperature rises rapidly above normal, the leucocytes more gradually increase far above normal, the vomiting and diarrhœa subside, so that within 12 hours after injection the animal may appear quite normal after a very severe intoxication.

Autopsy of a fatally poisoned animal shows extreme splanchnic congestion, especially apparent in the upper part of the small intestine, the mucosa of which is deep purple in color from congestion and hæmorrhage. Numerous necroses or hæmorrhages are present in the liver. The gall-bladder is œdematous; the stomach and intestines are filled with bile, intestinal juices and mucus.

B-Nucleo-proteid from Pancreas.

Fresh pancreas is chopped finely and ground in a mortar with sand, thoroughly stirred with twice its weight of distilled water and heated to the boiling point for 10 minutes. The interstitial fluid is poured off and filtered hot through ordinary filter paper; the residue is again heated to boiling with one-half the original volume of water. This is

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filtered hot and the residue squeezed in gauze. The filtrate, which is opalescent, is again filtered, acidified until it contains 1 per cent acetic acid, and a creamy white flocculent ppt. forms. The fluid is cooled in running water and the ppt. completely thrown out by the addition of an equal volume of 95 per cent alcohol. Place in ice-box for 6 to 12 hours. Filter or centrifuge off the supernatant fluid. The ppt. is redissolved in distilled water made slightly alkaline with dilute $NaCO_3$, and reprecipitated by being rendered slightly acid with dilute acetic acid. This process is repeated several times to get rid of soluble impurities. The precipitate is then washed with alcohol and ether and dried in a desiccator. Of this material .1 gm. per kilo produces a profound intoxication and sometimes death in young animals. It is dissolved in 10 or 20 cc. of very dilute $NaCO_3$ and injected intravenously.

Concentrated Proteid Poison.

The most concentrated toxic material has been obtained from autolyzing pancreas. Ground fresh pancreas is mixed with twice its weight of distilled water made slightly alkaline to litmus with $NaCO_3$. Chloroform is added and the mixture covered with toluol. It is placed in the incubator and digested at body temperature for 12 to 24 hours, being shaken at intervals. It is then made acid to litmus, boiled for 10 minutes and filtered hot through an ordinary filter paper. The clear yellow filtrate is made acid up to 2 per cent acetic acid, cooled in running water or in the ice-box, and left to stand 2 hours or longer. A flocculent precipitate forms. This is centrifuged and the supernatant slightly cloudy fluid is decanted. The precipitate is redissolved in dilute alkali and reprecipitated by acidifying with a few drops of very dilute (1 per cent) acetic acid. This is repeated until the decanted fluid gives no cloud with a drop of 1 per cent HCl. It is then washed with alcohol and ether and dried in a desiccator. This material is brownish, rather tough, easily soluble in warm dilute alkali, and has a tendency to jell on cooling in very dilute alkaline solutions. It gives a strong light-purple biuret reaction. In doses of .05 gm. per kilo intravenously or intraperitoneally it produces severe intoxication, which is usually lethal in young animals. The symptoms are those described as following an injection of fresh extract of pancreas, though the primary fall in blood-pressure is very slight.

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OLD AGE IN RELATION TO CELL-OVERGROWTH AND CANCER.*

By E. W. GOODPASTURE and G. B. WISLOCKI.

(From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins Medical School.)

The condition of multiple tumor formation in many organs and tissues of old dogs, which we shall describe, has an important significance, we believe, in relation to the age incidence of cancer in man and the lower animals. It illustrates strikingly the tendency of cells of senescent organs to take on new growth which may result in a malignant tumor. Although our series of animals is yet small, it is fairly complete, in that we have found tumor formation in nearly every glandular organ and in other tissues of the body.

In only one case was it possible for us to learn even the approximate age of the animal. This one had been in the possession of its owner for 14 years, and judging from appearances few of those in which we have found tumors were younger. We have been directed in our diagnosis of senility by familiar evidences, such as the loss of teeth, the presence of cataract and the appearance of decrepitude. Most of our animals, however, have shown only the absence of front teeth and wasting of others as a conspicuous sign. In no animal with extensive wasting and loss of teeth have we failed to find tumors in more than one organ. We may say also that we have never failed to find multiple tumors in any dog which we had classified as old before autopsy, whereas in hundreds of normal younger animals we have never observed a similar condition. All the old dogs were mongrels varying greatly in size and general features.

The uniform and coincident occurrence of the tumors, the fact that they are usually multiple in each organ, and a certain similarity in their mode of formation and growth make us feel that they are an expression of a common cause, the picture varying with the character of the tissue in which they occur. There are indications that the process begins as a regressive change, that is to say, certain cells first cease to function and later these areas take on new growth. This may be followed best in the thyroid. Here there is first a cessation of function in

* Abstract of a paper published in Jour. Med. Research, January, 1916.

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multiple foci consisting of a few acini. This is indicated by disintegration of colloid, and shrinking of the acini, the epithelial cells becoming larger owing to an increase of cytoplasm which is more granular, apparently, than normal. In some of these acini, before their lumina have completely disappeared and while atypically staining granules of colloid still persist, we find evidence already of beginning proliferation in the increase in the number of cells at points along the epithelial linings. Later the former acinus becomes a solid column of epithelium. The atrophic area is thus converted into a small tumor which increases in size both by proliferation of its own cells and by coalescing with other similar areas.

Though we may not follow with equal clearness the progress of these changes in all the organs, we do find in most instances quite comparable phenomena. In the ovary a degeneration of ova, in the testicle absence of spermatogenesis, in the liver atrophy of bile capillaries, and an absence of bile formation in the tumors, atrophy of the adrenal cortex, and of lymphoid tissue, accompany focal proliferative changes in these tissues. Both degenerative and proliferative changes are usually multiple in each organ, and we do not often find proliferation without evidences of degeneration.

Thus we are led to the interpretation that proliferation leading to tumor formation occurs in these cases in the cells of functionally involuting tissues; and, since the changes occur simultaneously in so many parts of the body, it is only natural to assume a common cause for their origin. We can imagine no other than senescence. Assuming, however, an equal age for these animals, we do not find that each organ in the various cases presents corresponding changes, nor are the same organs affected in each instance. This is to be explained, we think, by a variable absolute longevity of organs and tissues of an individual. As the individual longevity of different species varies tremendously, and as the functional life of certain organs of the same individual is relatively short, so the period of functional existence of each organ and tissue of different individuals of the same species probably has its natural limit, which may be shortened, or lengthened perhaps, by circumstances in the individual life. Consequently, an organ of one individual may earlier show evidences of disintegration than the same organ of another, and with the disintegration a tendency to proliferate.

In a general way the process seems to us to be a mode of disorganization of the individual, a coincident involution of constituent groups of units, units, which even at the expense of the individual sustained

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by their harmonious function, may under certain conditions strive to perpetuate their own life as more or less independent organisms when the natural period of the ability to function expires.

All the new growths we have described, except an adrenal medulla tumor which metastasized to the liver, were benign, in the sense that they did not extensively invade surrounding structures, nor metastasize. Whether they would eventually exhibit these malignant characters, and in what proportion, our series is too small to permit us to say. Surgical pathology has taught us, however, that such apparently benign overgrowths as senile parenchymatous hypertrophy and intra-cystic papilloma of the breast, both of which have a maximal incidence during functional involution of the gland, are dangerous precancerous lesions. Certainly the histological evidences of rapid growth, such as some of the above described tumors in dogs present (very numerous mitotic figures, variations in size, shape, and staining reactions of the cells) would indicate the possibility of rapid extension.

We have purposely made no attempt to classify the various tumor forms, preferring to look upon them simply as manifestations of a progressive process rather than as more or less distinct morphological units.

The following chart indicates the occurrence of tumors in various organs of each animal:

ORGANS.

Dog No.	Sex.	Liver.	Gall-bladder.	Stomach.	Pancreas.	Parotid.	Submaxillary.	Spleen.	Adrenals.	Testes.	Prostate.	Ovary.	Breast.	Thyroid.	Thymus.	Hypophysis.	Skin.	Subcut. tissue.	Blood vessels.	Bladder.
1	F	T	..	..	..	..	..	T	T	..	..	T	..	T	..	..	..	T	..	..
2	F	T	T	T	..	..	..	T	T	..	..	T	..	T	..	..	..	T	..	..
3	F	T	T	T	..	..	..	..	T	..	..	T	..	..	..	..	..	..	..	..
4	F	T	..	..	..	..	..	T	T	..	..	T	T	..	..	..	..	..	..	..
5	F	..	T	T	..	..	..	T	T	..	..	T	..	..	..	..	..	..	..	..
6	F	T	T	..	..	..	..	T	T	..	..	..	T	..	..	..	..	..	..	..
7	F	T	..	..	..	..	..	T	T	..	..	..	..	..	..	..	..	..	..	..
8	M	T	..	..	T	..	..	T	T	..	T	..	..	..	..	T	..	T	..	..
9	M	T	T	..	..	..	..	T	T	..	T	..	..	..	..	..	T	..	T	T
10	M	T	..	..	..	..	..	T	T	..	T	..	..	..	..	..	..	..	..	..
11	M	T	T	..	..	..	..	T	T	..	T	..	..	T	T	..	..	..	..	..
12	M	T	..	T	..	..	..	..	T	..	T	..	..	..	..	..	..	..	..	..
13	M	T	T	T	..	T	T	T	T	T	T	..	..	T	..	..	..	T	..	..
14	M	T	T	..	..	..	T	T	..	..	T	..	..	..	..	..	..	..	..	..
15	M	T	..	..	..	..	..	T	T	T	T	..	..	T	..	..	..	..	..	..
15	15	14	8	5	1	1	2	13	14	2	8	5	2	5	1	1	1	4	1	1

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THE EFFECT OF REMOVAL OF THE SPLEEN UPON THE METABOLISM IN DOGS. PRELIMINARY REPORT.

By J. H. KING.

(From the Hunterian Laboratory of Experimental Pathology and the Laboratory of the Chemical Division of the Medical Clinic.)

The object of the experiments briefly reported here was to ascertain what effect removal of the spleen would have upon the general metabolism in dogs. Animals of about the same weight were chosen and fed upon a diet which was calculated to bring them as nearly as possible into nitrogenous equilibrium. The various factors of metabolism were then studied for a period of days on a known diet. At the conclusion of this period the spleens were removed, and after time had been allowed for complete recovery from the operation, the metabolic studies were continued. The animals were upon the same diet as in the preliminary period.

The results may be summarized briefly as follows:

Nitrogenous Metabolism.—There is slight increase in the daily average output of total nitrogen after removal of the spleen. The increase, while greater than that shown in the control dog, is not of sufficient degree to indicate any important disturbance in the nitrogen balance. The urea fraction shows no constant change, the variations being practically within the normal limits. There occurred a slight, actual increase in the output of ammonia after splenectomy.

Viewed as a whole, the results of these experiments indicate that no disturbance of importance occurs in the metabolism of the proteins after the spleen has been removed from participation in the body metabolism. Goldschmidt and Pierce, as well as many other investigators, have reached similar conclusions.

Carbohydrate Metabolism.—The assimilation limit for dextrose, given in aqueous solution by the stomach tube, was not changed after splenectomy. Furthermore, the percentage of sugar in the blood was not disturbed by removal of the spleen. Hence it must be concluded that the spleen has no apparent effect upon the metabolism of the carbohydrates. This, however, does not exclude the possibility that the spleen and pancreas may be correlated.

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The interesting results of Sweet and Ellis, showing that after ligation of the pancreatic ducts in dogs, the spleen undergoes marked atrophy, make it probable that these organs are correlated in some of their functions.

Fat Metabolism.—After splenectomy there occurs a decrease in the percentage of the average total fats eliminated in the fæces (*i. e.*, the percentage of total fats to the output of fæces). The average natural fat percentage of the total fats remains the same after as before removal of the spleen. The free fatty acid fraction of the total fats is considerably increased after splenectomy, whereas the bound fatty-acid fractions show but little change. The blood lipase remains practically constant.

There is evidence, therefore, that the spleen takes some part in the fat metabolism, controlling to some degree the absorption of fats as well as the elimination of fatty acids.

The Mineral Metabolism.—A study was made of the chloride and calcium elimination after splenectomy. A considerable decrease in the chloride output was found in the urine. Variations in the amount of urine voided were not sufficient to account for the difference.

An interesting disturbance in the calcium output was observed. After splenectomy there occurred practically no changes in the fraction of calcium put out in the urine, but the fraction in the fæces was very definitely increased, entirely out of proportion to the difference in the average output of fæcal bulk.

The significance of this increased elimination of calcium is not at once apparent. Whether it stands in relation to the increased output of fatty acids, being eliminated as soaps, remains to be answered by further investigation.

Purin Metabolism.—During these experiments, the animals were put on a milk diet, and the elimination of endogenous uric acid was studied. No variation of any moment was found. The body apparently handles the metabolism of its endogenous uric acid just as efficiently without as with the aid of the spleen.

Discussion.—In a general sense, it can be said the metabolic processes of the body are but little influenced by removal of the spleen. The most striking changes are in the fat metabolism. Here, after splenectomy, there occurs an increase in the fats and cholesterin in the blood, together with an increased absorption of fats and an increased elimination of fatty acids. This, as has been pointed out in a previous paper, results in giving to the blood an increased efficiency against hæmolytic

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agents, and explains, to some extent, the improvement following splenectomy in hæmolytic types of anæmia. The increased elimination of calcium following splenectomy is interesting, and suggests that this loss of calcium to the body might stand in some causal relation to the clinical tendency of these cases towards hæmorrhages. The calcium disturbance, however, can hardly be of very great moment, since it has been found that puppies, from which the spleen has been removed, grow just as rapidly and to the same adult skeletal type as normal controls from the same litter.

The results of this study do not bring to light any group of findings which can be correlated into a clinical symptom-complex dependent upon a loss of function of the spleen.

A fuller and detailed report of these experiments will be published in the near future.

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THE EFFECT OF REMOVAL OF THE SPLEEN UPON BLOOD TRANSFUSION.

By J. H. KING, B. M. BERNHEIM and A. T. JONES.

(*From the Hunterian Laboratory of Experimental Pathology.*)

The changes which occur in the fat and lipoid content of the blood, after removal of the spleen, giving to it increased resistance against hæmolytic agents, as well as the improvement in the blood picture in certain types of hæmolytic anæmias after splenectomy, raised the question whether animals, after their spleens had been removed, might retain transfused blood longer than normal controls.

Dogs were the animals chosen for investigation and the transfusions were done by the indirect method.

SERIES I.—*Transfusions from one normal to another normal dog.* From 150 to 190 cc. of blood were transfused, causing a considerable plethora ranging from 1,000,000 to 2,000,000. This plethora diminished rapidly, with the result that the normal blood count reappeared at the end of 48 hours. One case showed a marked hæmoglobinuria.

SERIES II.—*Transfusion from a normal dog into a splenectomized dog.* The results in this series were indeed striking. Amounts of blood ranging from 100 to 125 cc. were transfused by the same method, causing a well marked plethora. In contrast to what occurred in Series I, this plethora continued very much longer, so that the animal's blood returned to its value before transfusion only after some 16 to 24 days.

SERIES III.—*Transfusion from a splenectomized dog into a normal dog.* About 100 cc. of blood from splenectomized animals were transfused into normal animals. There resulted a plethora, which lasted on an average for from 2 to 4 days; after this interval the dog's blood resumed the same numerical values as before operation.

No hæmoglobinuria or hæmaturia occurred, showing that the blood of a splenectomized animal does not possess hæmolyzing properties.

Discussion.—When the spleen is removed from the body there appears to result an increased power of retaining transfused blood. Splenectomized dogs retain this increase in the R. B. C. and Hb. for periods of from 16 to 24 days, in contrast to a 1 to 2 days' period for normal controls. This increased ability on the part of the body after splenectomy to retain blood for a long time may have great practical importance.

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It has been found that splenectomy will initiate a remission in pernicious anæmia when all other means fail. The regeneration of blood which follows indicates that the bone-marrow is relieved of some great strain. Furthermore, the change from increased values of the urobilin coefficient in the fæces to normal values, following splenectomy in pernicious anæmias, suggests that the hæmolyzing factor of this disease has been, at least, temporarily inhibited. It would seem unreasonable to expect a bone-marrow, which has been under such a great strain as pernicious anæmia imposes upon it, not to show traces of its previous decompensation, even after the disease had been arrested, temporarily, at least, by splenectomy. It would appear just as irrational to allow a diseased bone-marrow which has been relieved of its strain to go without supportive treatment as to neglect to treat, from time to time, a diseased heart which has been restored to compensation. Just as in the latter case, when signs of a decompensation appear, they are combated by rational therapy, so in the treatment of pernicious anæmia cases after splenectomy, it is incumbent upon the physician to watch for signs of a returning weakness of the bone-marrow, and to apply therapeutic measures at once.

As long as the blood-count is increasing and remains reasonably high, and the urobilin values stay within normal limits, there need be little concern. When the latter begins to increase and the blood counts fall, then the bone-marrow needs help. Medical therapy may be often hopelessly inadequate. Transfusions appear to offer us the best means of warding off a return of the disease. A case of pernicious anæmia recently treated in the hospital by this therapy showed that after splenectomy the benefits of transfusion were retained much longer than was the case before removal of this organ. Repeated transfusions brought the blood in this case up to normal values.

Indeed, it may be hoped that repeated transfusions at regular intervals may prevent any return of the disease. Considering the undisputed fatality of this disease, such a therapeutic procedure should be given a thorough trial.

Should clinical experience substantiate the claims of experimental medicine in regard to the efficacy of repeated transfusion after splenectomy in the therapy of the pernicious anæmia, a great advance will have been made in combating this disease.

A fuller and more detailed report of these experiments will be published later.

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STUDIES ON PARATHYROID TETANY.*

By D. WRIGHT WILSON, THORNTON STEARNS, J. H. JANNEY, Jr., and MADGE DeG. THURLOW.

(From the Laboratory of Physiological Chemistry and the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins University, Baltimore.)

The extirpation of the parathyroid glands from animals causes the development of a condition of tetany with accompanying abnormalities of metabolism about which our knowledge is but fragmentary. Certain data derived from metabolic studies have suggested that a condition of acidosis results. The evidence in the past, however, has been rather conflicting. The possibility that there may be a condition of, or tendency toward, an alkalosis after parathyroidectomy has received no attention. This hypothesis is interesting in connection with the following facts. Alkalies are known to increase the symptoms of tetany. Sodium bicarbonate has been shown to be distinctly harmful, and sodium and potassium acetates apparently act in the same way. Sodium chloride is innocuous in isotonic solution.

We have shown that the intravenous injections of N/3.7 or N/7 hydrochloric acid solutions relieved parathyroid tetany in dogs. The period elapsing before the return of the symptoms varied somewhat according to the amount of acid introduced, but in some cases extended over several days.

In support of the evidence offered in favor of acid injections, we have observed relief in several cases when acid was introduced by the mouth. The difficulties of this procedure, however, render it of uncertain value. In tetany the stomachs of most dogs are so sensitive that no material can be retained. We were fortunate to obtain one animal which, by

* This article is an abstract of the following papers: (1) The Effect of Acid Administration on Parathyroid Tetany. D. Wright Wilson, Thornton Stearns, and J. H. Janney, Jr.; Journ. Biol. Chem., XXI, 1915, 169. (2) The Acid-base Equilibria in the Blood after Parathyroidectomy. D. Wright Wilson, Thornton Stearns, and Madge DeG. Thurlow; *Ibid.*, XXIII, 1915, 89. (3) The Excretion of Acids and Ammonia after Parathyroidectomy. D. Wright Wilson, Thornton Stearns, and J. H. Janney; *Ibid.*, XXIII, 1915, 123.

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careful manipulation, retained most of the acid introduced, and during the period of acid ingestion (5 days) showed no typical tetany. The symptoms became acute later when sodium bicarbonate was given.

The relief from parathyroid tetany observed after the administration of acids suggests the possibility of a peculiar abnormality of metabolism whereby the normal equilibrium of acids and bases in the body is disturbed, resulting in a relative increase in the amount of base. This condition may quite naturally be termed alkalosis by analogy to the familar condition called acidosis. In agreement with the more exact definitions of acidosis, we may designate alkalosis as a pathological condition in which the basic radicles in the blood are relatively increased over the acid radicles, disregarding carbonic acid. This definition does not specify whether the bases are absolutely increased or the acids not CO_2 are decreased, or whether both phenomena occur. Nor does it imply that the blood in the body is more alkaline than usual, for an increased tension of CO_2 may neutralize any tendency towards a decreased hydrogen-ion concentration and maintain a final reaction differing little from the normal.

Most of the methods used in the past in the study of acidosis are available for the investigation of a condition such as is described above. As in acidosis, the problem is complicated by the fact that the variations in the reaction of the blood are never very great and have always been difficult to determine. As the ordinary titration procedures are unsatisfactory, most of the methods of study have been indirect.

Several methods have been developed recently which should be valuable in furnishing the necessary data. Barcroft and his collaborators have shown that the dissociation of oxyhæmoglobin may serve as a very sensitive index to variations in the reaction of the blood. A new method for the rapid determination of the hydrogen-ion concentration of the blood has recently been devised by Levy, Rowntree, and Marriott, which is sufficiently delicate to record slight changes in the reaction of the blood.

When determined at a constant temperature and under comparable conditions the changes in the values of the dissociation constant of oxyhæmoglobin may indicate variations in the hydrogen-ion concentration of the blood examined. Two methods of study are readily available. Variations in the actual hydrogen-ion concentration of the blood as it exists in the body may be ascertained by determining the values of the dissociation constant of oxyhæmoglobin in bloods containing the

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amount of carbon dioxide they held when in the body, or, practically, in bloods brought into equilibrium with a pressure of carbon dioxide equal to the alveolar carbon-dioxide tension.

The second procedure consists in bringing the blood into equilibrium with a constant tension of carbon dioxide and a suitable pressure of oxygen and determining K. This method eliminates the neutralizing action of the carbonic acid which varies with the alveolar carbon-dioxide tension. The resulting values should show variations which are comparable to the values obtained by titration methods and indicate changes in the "non-volatile" acid-base equilibrium or the "reserve alkalinity." Variations from the normal indicate acidosis or alkalosis conditions.

In most of the experiments reported below, the values of the dissociation constant of oxyhæmoglobin were determined by this procedure, in order to determine whether acidosis or alkalosis conditions existed. A few determinations were made, the first method being employed.

A single protocol may serve as an example of the results that we have obtained.

Experiment 42.—This animal did not develop acute tetany for several days after the operation, although mild tremors were apparent on the second day. The rise and fall in the values of K during the first 4 days of the experiment without the development of acute tetany emphasize similar observations in previous experiments. Notwithstanding the more pronounced tremors on the 27th, a considerable alkalosis persisted during the day, increasing to a maximum in the evening. The value of K dropped quickly after the injection of $CaCl_2$ solution, but did not return to normal. It was slightly lower on the following day, but was high again on the next.

Another comparison was made of the variations in the reaction of the blood brought into equilibrium with a gas mixture containing CO_2 at a pressure approximately that of the alveolar air. On the 26th, when the value of K by the regular method was still somewhat above normal, the value of K with blood containing the requisite amount of CO_2 was 0.00019. On the following day, although the alveolar carbon-dioxide pressure was considerably higher, a value of 0.00031 was obtained. Thus, in spite of the increased content of carbonic acid, the blood was pleonectic, or more alkaline than on the previous day. This decreased hydrogen-ion concentration of the blood in the body suggests an increased irritability of the respiratory center.

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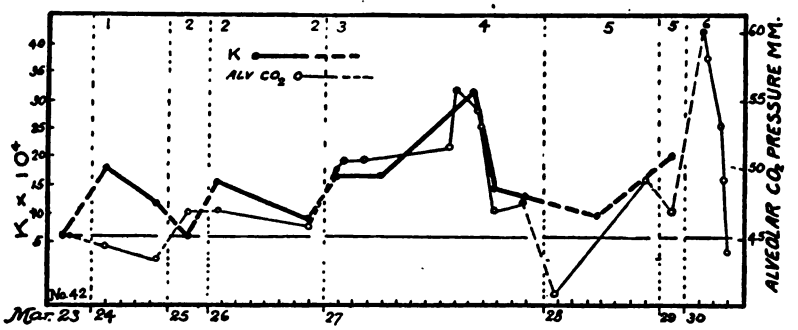
The most noticeable variations in the alveolar carbon-dioxide tensions occurred during the extreme attacks of tetany, when they usually rose rapidly to a maximum and then fell rapidly. The Plesch method was used to obtain samples of the alveolar air. The analyses were carried out with a small Haldane gas analysis apparatus.

The characteristic rise and fall in the alveolar CO_2 pressure during periods of acute tetany may be observed in most of the experiments. The pressure rose gradually as the tremors became more severe, though little effect on the respiration was observed. We did not determine whether the ventilation was increased. Soon after the acute attack began, panting commenced and the alveolar CO_2 pressure dropped more or less rapidly to a value below normal. Later there was often a con-



Experiment 42.—Operation, March 23. 1. Quiet; no tremors. 2. Fine tremors. 3. Moderate tremors. 4. Injected $CaCl_2$ solution. 5. Mild tremors. 6. Acute tetany.

dition of depression and the tremors had nearly or completely disappeared.

The complication introduced by the muscle tremors renders the high values of little importance as indicating a possible alkalosis. They probably represent a piling up of CO_2 faster than it can be removed. It is interesting in this connection, however, to note the high pressures which may develop before the gross indications of hyperpnea, *i. e.*, panting, develop. The alveolar CO_2 tension may rise 10 mm. before panting starts. Even more suggestive are the numerous observations where the alveolar CO_2 tensions rose to values considerably above normal and remained for hours without any indications of increased stimulation of the respiratory center or excessive muscular activity.

It would seem that these values could hardly be attributed to the muscular activity. They might be due to a depression of the respiratory

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center, which would naturally result in an increased CO_2 tension. But in one of the most striking experiments (No. 42), the value of the dissociation constant of oxyhæmoglobin indicates that the respiratory center was, indeed, unusually irritable and the hydrogen-ion concentration of the blood in the body definitely decreased, resulting in a condition of pleonexy. These increased alveolar CO_2 tensions may, therefore, indicate that a condition of alkalosis was present at these times.

The low tensions observed after the attacks may be ascribed to the acidosis conditions resulting from the extreme muscle work. Similar low values have often been observed after muscular activity and ascribed to a temporary acidosis caused by the presence of lactic acid formed on account of the lack of an adequate oxygen supply to the muscles during activity.

The injection of acids into the blood-stream might naturally be expected to cause variation in the " non-volatile " acid-base equilibrium. Evidence supporting this was obtained. A fall in the alveolar CO_2 pressure after calcium administration was noted whenever this procedure was used. This was accompanied by a decrease in the values of the dissociation constant of oxyhæmoglobin.

We have endeavored to supplement our findings by means of a method for the determination of the hydrogen-ion concentration of the blood devised by Levy, Rowntree, and Marriott. The method consists in dialyzing blood in celloidin sacs against neutral salt solution and determining the reaction of the dialysate by color comparisons with an indicator. The procedure is simple and trustworthy, if care is taken to work with controlled solutions in a room free from fumes of acids or alkalies. Bloods were examined as they came from the veins, and again after shaking out the excess CO_2. Variations in the " non-volatile " acid-base equilibrium should become apparent with the second procedure.

The normal variations of P_H, using blood as drawn from the vein, were found to be from 7.3 to 7.4. After the blood had been brought into equilibrium with the air, the P_H ranged from 7.6 to 7.75 in different normal animals.

Any variations in P_H in the blood as it came from the parathyroidectomized animals were evidently too slight to be recorded with certainty by this method. After the blood had been shaken, however, slight but definite changes were noted. In all cases examined in which tetany developed, an increased alkalinity was observed after removal of the excess of CO_2, the values of P_H ranging from 7.75 to 8.00. With the

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development of tetany, the values returned to normal. These variations run roughly parallel to those indicated by the values of K.

A considerable acidosis was observed in one experiment after the injection of acid, in agreement with the results of the alveolar CO_2 and oxyhæmoglobin dissociation methods. After the CO_2 had been shaken out, the P_H was 7.40 instead of the normal value, 7.65. Even the blood dialyzed directly showed an appreciable increase in hydrogen-ion concentration.

The experiments outlined above have furnished evidence to support the view that, after the removal of the parathyroid glands from dogs, there may develop a condition of alkalosis. This alkalosis tends to be counteracted by the tetany which soon becomes manifest. Acid metabolic products are apparently formed during tetany which neutralize the excess of bases and may even produce an acidosis of varying duration. During the acidosis periods following the acute attacks, the gross symptoms of tetany are usually less evident.

Numerous observations have been made on the urine of dogs after parathyroidectomy, which suggest that a state of acidosis exists. Acetoacetic and lactic acids have sometimes been found. Other phenomena, however, fail to support this view and they may be explained even more easily on the assumption that there is a relative excess of alkali in the body—an alkalosis. That both conditions may occur at different periods in the course of tetany seems probable.

We have shown that acids, when administered to dogs in parathyroid tetany, relieve the symptoms. A relative excess of alkali (neglecting CO_2) in the blood at certain periods after parathyroidectomy is indicated by the values of the dissociation constant of oxyhæmoglobin, alveolar CO_2 pressure, and the hydrogen-ion concentration of the blood. These studies make it appear that the alkalosis is primary, and that the acidosis develops only secondarily during the attacks of tetany and may give place to another alkalosis period, unless the tetany is sufficient to maintain it. Data are presented concerning the ammonia and acid excretion and the hydrogen-ion concentration of the urine, which may furnish additional details concerning the variations taking place within the body.

Dogs were placed in metabolism cages and the urine was collected in two periods daily by catheterization, extreme care being taken to guard against cystitis. A sterile catheter and vaginal dilator were used after a thorough washing of the external surfaces and the vagina with

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warm sterile water or a very dilute bichloride solution. No food was given the animals after the operations. This procedure may have diminished the variations in our findings on account of the tendency toward acidosis due to fasting and the less favorable condition for tetany development. After a suitable fore-period, the parathyroids were removed with varying amounts of thyroid tissue and the animals kept under observation. Water was usually given through the stomach tube twice daily.

The following methods were used: Total nitrogen, Kjeldahl; ammonia, Folin; acid excretion, Henderson and Adler; hydrogen-ion concentration, Henderson. Experiments were carried out on 6 dogs from which the parathyroid glands were removed together with most of the thyroid tissue.

The data presented show, in general, that after parathyroidectomy there is a marked diminution in the excretion of acids and ammonia, accompanied by a decrease in the ratio of NH_3—N to total N, and in the hydrogen-ion concentration of the urine. After the development of tetany, the excretion of acids and ammonia increases as well as the ammonia ratio and the hydrogen-ion concentration of the urine. The following facts may be considered in attempting an explanation for these variations:

Studies on the urine in conditions of acidosis have shown that characteristic changes occur. Walter observed, many years ago, that the ammonia output was increased after the ingestion of acids. From the accumulated data, especially the newer and more exact observations of Henderson and others, the characteristic urine changes in acidosis may now be described as an increase in ammonia and its relation to total nitrogen, increased acidity both as expressed by titration values and the hydrogen-ion concentration and increased phosphate elimination, unless the phosphate store is depleted. The excretion of ammonia, acids, and phosphates may run roughly parallel for a time.

With the ingestion of alkali, the acidity falls and the urine may become alkaline. A decrease in the ammonia output is characteristic. Janney was able to cause the daily ammonia elimination to diminish to 0.04 gm., which was 0.4 per cent of the total nitrogen, by the ingestion of sodium bicarbonate. These variations in the excretion of ammonia are so characteristic that they have been taken as an index of changes occurring within the body. As a part of the mechanism for the maintenance of neutrality within the body, ammonia combines

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with a portion of the acids formed and is excreted. In acidosis, when an excess of acids is formed, the ammonia output is increased; when there is an excess of "fixed alkali" in the body, as after excessive ingestion of sodium bicarbonate, the ammonia elimination is diminished.

These relationships might possibly be altered by an unusual abnormality in kidney function. Acidosis conditions due to renal changes have been suggested by Henderson and Palmer. No indications of renal insufficiency have been noted after parathyroidectomy. We have found normal values for the blood urea and the phthalein excretion during tetany in two of our animals.

Analyzed in accordance with the observations mentioned above, the data presented indicate that there is a relative excess of "fixed alkali" in the blood, *i. e.*, an alkalosis, soon after parathyroidectomy. This alkalosis is apparently not due to an excess of circulating ammonia, as the ammonia excretion is at a minimum during the periods of decreased acidity of the urine. The ratio of NH_3—N to total N, may be unusually low at the same time. Also, there is no satisfactory evidence to show that the ammonia content of the blood is above normal. The variations are strikingly similar to those observed after the ingestion of sodium bicarbonate.

With the development of tetany, the urine picture changes quickly. The increased excretion of acids and ammonia, together with high values of the ammonia ratio, suggests an acidosis. The increased acidity is probably due (in part) to the excretion of the lactic acid formed in the muscles during tetany.

Summary.

The tetany which develops after parathyroidectomy may be relieved by the administration of acids. This observation has led to a series of studies from the data of which the following conclusions have been drawn.

After parathyroidectomy a condition of alkalosis may develop which is neutralized by acid products formed by the muscular activity incident to tetany. An acidosis condition may result after periods of acute tetany. Periodic variations in the "non-volatile" acid-base equilibrium seem to accompany the periodic attacks.

The acidosis condition resulting from acute tetany or the injection of acid is associated with relief from tetany.

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Calcium salts, when injected into animals in tetany, lower the value of the dissociation constant of oxyhæmoglobin and the alveolar CO_2 pressure, an effect similar to that brought about by the introduction of acids.

The above conclusions were reached from a study of the variations of the values of the dissociation constant of oxyhæmoglobin, the alveolar CO_2 pressure, and the hydrogen-ion concentration of the blood from dogs subjected to parathyroidectomy.

After parathyroidectomy in dogs there is usually a sudden diminution in the excretion of acids and ammonia and a decrease in the ammonia ratio and the hydrogen-ion concentration of the urine. With the development of tetany, the elimination of acids and ammonia increases, accompanied by increased values of the ammonia ratio and the hydrogen-ion concentration of the urine.

These variations may indicate that an alkalosis condition results after parathyroidectomy, but is neutralized by the tetany which develops. After acute or chronic tetany an acidosis may occur.

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SOME OBSERVATIONS ON THE EFFECT OF FEEDING GLANDS OF INTERNAL SECRETION TO CHICKS.

By M. C. WINTERNITZ.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

In 1914 Cushing and Goetsch showed that the feeding of dried extract of anterior lobe of bovine hypophysis to white rats has a markedly stimulating effect on the growth and development of the reproductive glands of both sexes. Furthermore, it tends to cause early and frequent breeding.

These experiments were repeated with chicks in the hope of obtaining a more practicable application of these phenomena.*

The following three series may be of interest in spite of their conflicting results.

SERIES I.—Twenty-two white leghorn chicks were divided into two groups, 11 controls and 11 hypophysis-fed animals.

On May 21, when they were 23 days old, the feeding of dried hypophysis gland was begun.

Method.—The chicks were kept in separate bins and were given, except for the dried glands, exactly the same food. Their diet was that advised by the Department of Poultry Husbandry of the College of Agriculture of Cornell University, for white leghorn chicks. Very small amounts of the hypophysis were given. Twenty moist bread pills, thinly coated by rolling in a bowl containing about 250 mg. of the powdered gland, were fed daily. The chicks were weighed at varying intervals and the results may be seen in the accompanying chart.

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* Attempts to modify the growth of young chicks by feeding hypophysis have yielded various results. These are briefly summarized by Wulzen. The following is a quotation from her article: "The preponderance of the above evidence indicates that the pituitary body, either injected or ingested, is able to cause a diminution in rate of growth of young animals. I have been able to confirm . . . . the falling off in the weight of the animal and in length of bone following ingestion of anterior lobe of the pituitary body."

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CHART I.

WEIGHT IN POUNDS.

Date.	Control Chicks.	Hypophysis-Fed Chicks.
May 21	2 lbs. 14 oz.	2 lbs. 12 oz.
June 11	4 lbs. 12 oz.	6 lbs.
June 21	7 lbs. 6 oz.	9 lbs. 14 oz.
July 9	8 lbs. 14 oz.	12 lbs.
Oct. 11	22 lbs. 6 oz.	27 lbs. 7 oz.

Besides the difference in weight between the hypophysis-fed chicks and the controls, there was an equally surprising difference in their egg production. The first egg was laid by the hypophysis-fed chicks when they were 199 days old, the controls did not begin to lay until the 243d day of life. By February 1 the former had averaged 15 eggs apiece, the controls only one. As spring approached, the two groups tended to lay more equally; in March the hypophysis-fed chickens had 15 eggs each to their credit, the controls 6.

SERIES II.—In this series other glands of internal secretion as well as the pituitary were fed to different groups of black langshan chicks.

Each group, except the control, was fed 2 grains of the powdered gland daily. The birds were weighed collectively every week, beginning when they were 1 day old. The results may be seen from the following chart:

CHART II.

WEIGHT IN OUNCES.

Date.	Adrenal.	Hypophysis.	Control.	Ovary.	Thyroid.	Thymus.
Feb. 21	8	8	8	8	8	8
Feb. 28	11½	9½	9½	10½	9½	11½
March 7	15½	11½	12	13½	10½	15½
March 14	21	16½	17	21	14	20
March 21	27	24	22	25	20	26
March 29	36	32	28	32½	26	36½
April 5	41½	37	32½	39	30	39½

The only constant finding in this experiment was the delayed growth of the chicks that were fed thyroid. This was evident early in the experiment, and these chicks not only remained small but succumbed more quickly to nutritional disorders.

At the end of 7 weeks the experiment was discontinued, as a number of the chicks in each group had developed a curious pathological condition. They gradually lost their ability to stand and sprawled on the floor with their legs spread out helplessly. At first, when urged, they could get up and run a few steps, but in the later stages of the disease they could not use their legs at all and propelled themselves by fluttering their wings. In spite of this disability some lived for several weeks and showed remarkable activity. Several recovered when taken out of confinement and put outdoors. The disease first appeared among the chicks that received thyroid. In those that recovered the femurs were bent and presented a picture similar to the rachitic saber shin.

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SERIES III.—One hundred white leghorn chicks were divided into 10 lots and fed the following glands:

Lots.		Beginning when.	Gm. Daily.
1, 2 and 3..	Dried hypophysis (bovine)....	20 days old	1-4
4.....	Fresh hypophysis (pig).....	7 days old	10-20
5.....	Fresh adrenal (pig).....	7 days old	10-20
6.....	Fresh ovary (pig).....	7 days old	10-20
7.....	Fresh testes (pig).....	7 days old	10-20
8.....	Fresh thyroid (pig).....	7 days old	1
9.....	Fresh thymus (pig).....	7 days old	10-20
10.....	Control.		

The chicks were weighed weekly as shown in the following chart:

CHART III.

WEIGHT IN GRAMS.

Date.	Hypoph. Fresh.	Hypoph. No. 1.	Hypoph. No. 2.	Hypoph. No. 3.	Adrenal.	Ovary.	Testes.	Thymus.	Thyroid
April 24..	350	350	350	350	350	350	350	350	370
April 29..	460	480	460	430	480	460	460	470	460
May 5..	690	720	680	700	700	680	700	670	660
May 12..	950	1040	940	930	970	960	900	990	880
May 19..	1300	1350	1250	1210	1250	1270	1290	1280	900
May 26..	1600	1770	1590	1570	1630	1630	1680	1570	1120
June 2..	1800	1960	1840	1820	1800	1820	1920	1880	1220
June 9..	1860	2160	2010	2000	1950	1930	1820	1930	1480
June 16..	2100	2450	2340	2230	2280	2180	2050	2140	1670

As is evident from this chart, the various glands that were fed, except the thyroid, had very little effect upon the weight of the different groups. The thyroid-fed chicks gained less than the rest throughout the experiment and, as in the previous experiment, seemed less robust.

The marked changes apparently brought about by the administration of hypophysis in the first experiment is in great contrast to its inactivity in the subsequent ones, despite the fact that three separate brands of the dried hypophysis, as well as the fresh glands, from the pig were used.

The fact that the hypophysis varies in its activity at different times of the year and that it is inactive during the hibernating season may have a bearing upon the contradictory results cited above.

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SPONTANEOUS AND EXPERIMENTAL LEUKÆMIA IN THE FOWL.*

By H. C. SCHMEISSER.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

During the past three years a transmissible leukæmia of the fowl has come under observation.

In confirmation of the work of Ellermann and Bang, Hirschfeld and Jacoby, and Burkhardt, the disease has been successfully transmitted in the same species from the spontaneous case into the fifth generation by the intravenous and intraperitoneal injection of an organ emulsion.

Hirschfeld and Jacoby, and Burkhardt, obtained their original strain from Ellermann and Bang.

The transmission, reported above, is of special interest, as the strain originated in an animal absolutely unrelated to that of the previous investigators.

* A detailed report, including an abstract of the literature, a study of the blood and anatomy of the normal fowl and of the spontaneous case of leukæmia, as well as of the animals in which the disease was transmitted, may be found in: (1) The Johns Hopkins Hospital Reports, 1915, XVII (Illustrated). (2) Jour. Exp. Med., 1915, XXII, 820.

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STUDIES ON THE RELATION OF FOWL TYPHOID TO LEUKÆMIA OF THE FOWL.

By M. C. WINTERNITZ and H. C. SCHMEISSER.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

In 1897 Moore[1] published studies on an epidemic infectious disease of the fowl, which he designated Leukæmia and from which he isolated a bacterium which he believed was the etiological agent of the disease.

His work has been confirmed by subsequent observers who, however, have not regarded the condition as a true leukæmia. Recently, Theobald Smith[2] and his associate Ten Broeck have carefully investigated the organism isolated by Moore in 1897, as well as other strains of the same bacillus. On account of the features which it has in common with the human typhoid bacillus, among them its behavior toward carbohydrates and the agglutination reaction, they suggest that it be called the fowl typhoid bacillus.

On the other hand, a number of observers, chiefly Ellermann[3] and his associates, have reported detailed studies on a chronic disease of the fowl which simulates very closely human leukæmia. The analogy between this disease in the fowl and in man is still closer in one respect, in that no parasite has been demonstrated as the causative agent in either case. Ellermann, however, asserts that he has been able to reproduce the condition in the fowl by the injection of a cell-free Berkefeld filtrate of a blood or organ emulsion from a diseased fowl.

No attempt will be made to discuss the literature of these conditions. The former disease has been carefully reviewed in the articles by Theobald Smith and Ten Broeck, and the latter disease by Schmeisser[4] in his report on spontaneous and experimental leukæmia in the fowl.

An epidemic of an acute disease in the fowl was brought to our attention and in the investigation and experimental transmission of the condition certain interesting transitions were encountered which led us to believe that there might be a relationship between the acute disease described by Moore and subsequently called Fowl Typhoid and the chronic condition known as Chicken Leukæmia.

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Spontaneous Case.

During the fall of 1914 a disease appeared in a flock of Plymouth Rock fowls in Howard County, Md. About 10 per cent of the birds died. The disease was more severe in the pullets than in the older birds. Their combs and wattles became white and they emaciated rapidly. The fowls which the farmer opened were reported to have had enlarged livers. Two suspicious pullets were brought to the laboratory for observation. One of these died immediately on arrival. The following brief notes from the autopsy are recorded:

Autopsy. The fowl weighed 1120 gm. It was moderately emaciated and showed practically no subcutaneous fat. The cervical lymph glands were slightly enlarged, gray, and showed no interlobular fat. The liver was enlarged. It weighed 83 gm. Externally as well as on section the brown parenchyma showed a gray tracery. It was studded with white or pink, slightly opaque foci, about 1 mm. in diameter, and numerous pin-point hæmorrhages.

The spleen was enlarged; it weighed 3 gm. It was diffusely gray, both externally and on section.

The bone-marrow was hyperplastic and gray.

The heart muscle was studded with numerous small gray nodules.

Blood smears showed a leucocytosis. The ratio of the white to red blood cells was 1 to 3.5. The red blood cells varied slightly in size, shape and staining of both cytoplasm and nucleus.

The differential count showed a leucocytosis with an increase of polymorphonuclear leucocytes with rods and an almost equally marked increase in mononuclear cells.

Count of 300 cells:

Polymorphonuclear cells with eosinophilic rods	54.0%
Polymorphonuclear cells with eosinophilic granules	0.0%
Lymphocytes	5.3%
Large mononuclear cells	40.4%
Mast cells	0.0%
Unclassified cells	0.3%

Microscopic examination of the organs showed a great increase in the white blood cells in the vessels.

There was a diffuse or focal myelosis in all of the organs. This was most marked in the lymph glands, heart, liver and spleen. All types of marrow cells occurred. The large mononuclear and the mononuclear myelocyte with eosinophilic granules were the most prominent. They all showed numerous mitoses.

The liver cells were extensively degenerated and necrosed. The bone-marrow showed a marked hyperplasia. The large mononuclear and the mononuclear myelocyte with eosinophilic granules predominated.

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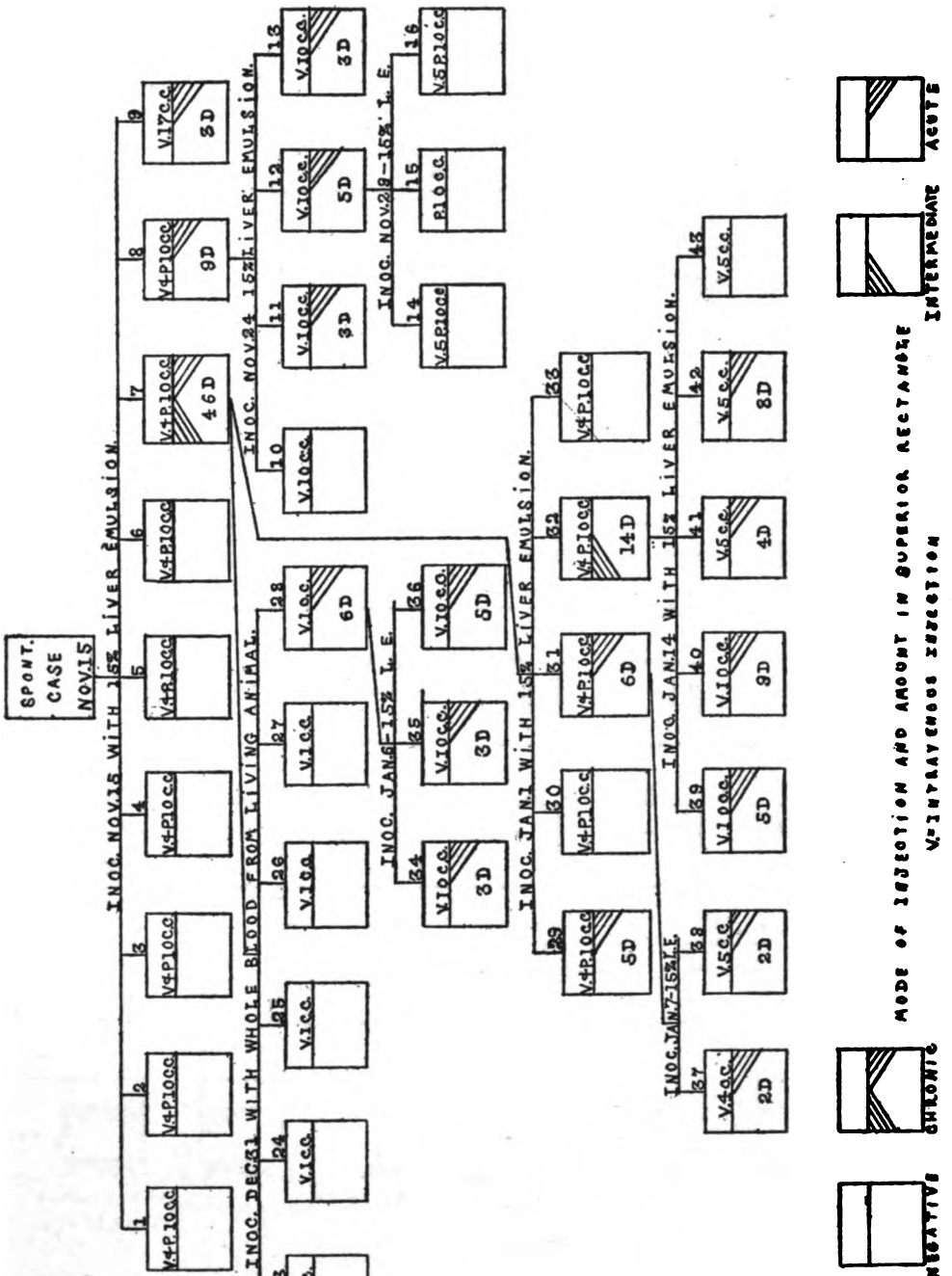
SPONT. CASE NOV.15
INOC. NOV.15 WITH 15% LIVER EMULSION.
INOC. DEC.21 WITH WHOLE BLOOD FROM LIVING ANIMAL.
INOC. JAN.6 1.5% L. E.
INOC. JAN.7 WITH 15% LIVER EMULSION.
INOC. JAN.14 WITH 15% LIVER EMULSION.
INOC. NOV.24 15% LIVER EMULSION.
INOC. NOV.28 - 15% L. E.
INOC. JAN.7-15% L.E.
MODE OF INJECTION AND AMOUNT IN SUPERIOR RECTANGLE
V. INTRAVENOUS INJECTION
P. INTRAPERITONEAL INJECT.
CHART I.
NEGATIVE
CHRONIC
INTERMEDIATE
ACUTE

Errata: Chart I, No. 29, should be *negative;* No. 16 should be *acute.*

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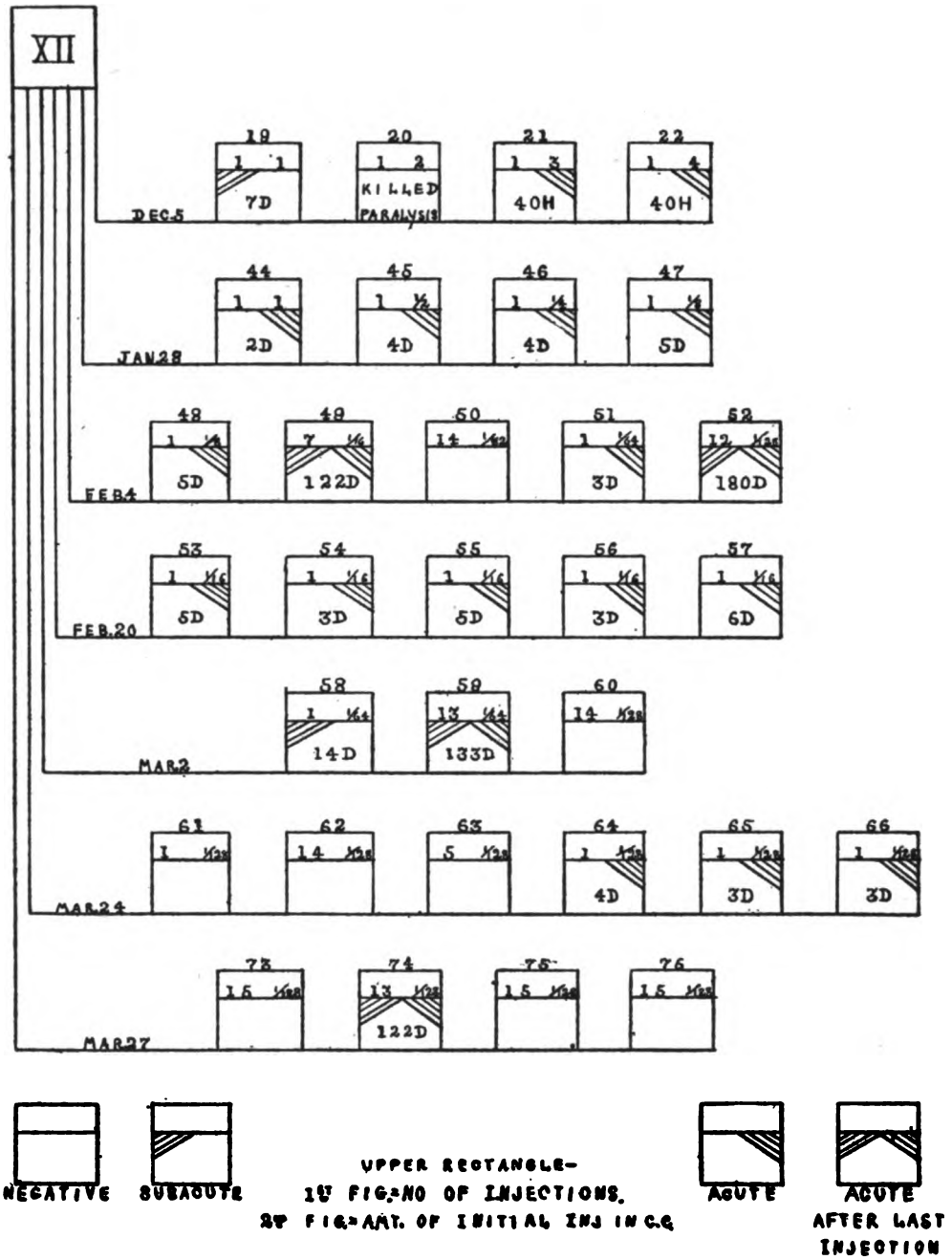

NEGATIVE SUBACUTE

UPPER RECTANGLE—
1ST FIG.=NO OF INJECTIONS.
2ND FIG.=AMT. OF INITIAL INJ IN C.C.

ACUTE ACUTE AFTER LAST INJECTION

CHART II.

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HYALINE DEGENERATION OF THE ISLANDS OF LANGERHANS IN PANCREATIC DIABETES.

By M. C. WINTERNITZ.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

The stimulus to this paper was a case of diabetes mellitus with changes in the islands of Langerhans that may aid in the interpretation of the histo-pathology of the pancreas in this disease.

Literature.

No attempt will be made to review the literature, which is very well presented in such articles as those of Opie,[2] Sauerbeck,[3] and more recently of Allen.[3] It will suffice here to present a brief outline of the more important views.

The articles of the literature may be arbitrarily divided into two groups: Firstly, those dealing with the experimental disease in animals; and secondly, those dealing with the histo-pathology of the human pancreas in diabetes mellitus.

(1) *Experimental Diabetes in Animals.*—Many attempts have been made to determine the relationship of changes in the pancreas to experimental glycosuria, and many species of animals have been used. All of these experiments have had as their object the ultimate destruction of the acinar and the preservation of the insular tissue of the pancreas. The results have been extremely conflicting, and no definite conclusions could be drawn from the extensive studies without a review of the entire subject. This has been accomplished by Allen, and the following abstract is quoted from his summary:

In rabbits and guinea-pigs the pancreas may be reduced to nothing but islets without diabetes; but true diabetes has not been produced in these animals by any method; it is not known whether they are susceptible to the condition. . . . . In dogs it has not yet been demonstrated by serial section that the animal is free from diabetes at a time when nothing remains of the pancreas but islet tissue. . . . . Diabetes has never been observed with well-preserved islands. Absence of diabetes has never been observed in absence of islands with the single exception reported by Pratt.

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In contrast with the above, the experiments of Allen are of importance. He removed nine-tenths of the pancreas in a series of animals and left the remnant in connection with the duct. This resulted in a diabetes which, at first, was relatively mild, but which increased in severity until there was a complete inability to utilize dextrose. At the outset the islet showed no visible alterations; later, a degeneration occurred which involved these—they showed loss of cells, deficiency of cytoplasm in the remaining cells, nuclear degeneration and, finally, there was a complete disappearance of the islets. In typical cases, aside from accidental changes, the acini remained normal throughout.

If these findings are confirmed, they furnish important evidence that the insular tissue, in contrast to the acinar tissue of the pancreas is intimately associated with the utilization of dextrose in the body.*

(2) *Studies in the Histo-Pathology of the Pancreas in Diabetes.*—All investigators have had the same problem to face, namely, Is the histo-pathology of the diabetic pancreas distinctive? In other words, Can the pathologist, without reference to the clinical history be sure of the diagnosis of diabetes from histological examination of the pancreas?

Instead of reviewing the various theories, an attempt will be made to set forth the conflicting problems met with in the histo-pathological correlation of the disease.

I. Diabetes may occur without any definite qualitative changes in the pancreas.

Many authors resort to a functional hypothesis for the explanation of these cases and blame the deficiency, either upon the acinar or insular tissue, according to the theory which they uphold.

These cases seem to offer definite evidence that lesions of the pancreas are not secondary to the malassimilation of carbohydrates.

This group may include certain cases of glycosuria dependent upon changes in the nervous system or disturbances in ductless glands other than the pancreas, associated with carbohydrate metabolism.

To a subdivision of this group of cases of diabetes without qualitative changes in the pancreas belong those cases which show only quantitative change in the insular tissue. This aspect of the histo-pathology of the subject has been particularly emphasized by Opie, Heiberg,[4] Weichselbaum,[5] etc. Heiberg determined that there are 130 islands

* Since this paper was written, an article by Homans in the Journal of Medical Research, 1915, Vol. XXXIII, No. 1, confirms these findings.

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per 50 cu. mm. in a given portion of the normal pancreas, and that this number of islands is reduced to from 30 to 40 per 50 cu. mm. in the same area of a diabetic gland. He concludes that this estimation of the number of islands offers a method for the absolute anatomical diagnosis of diabetes.

In general, Heiberg's observations have been confirmed by Weichselbaum. The latter, however, emphasizes certain qualitative changes, such as hydropic degeneration, etc., of the islands. He believes that if these qualitative changes are not present, the process has been of long standing and that the previously affected islands have disappeared in the earlier stages of the disease. Weichselbaum emphasizes the power of the insular tissue to regenerate. He thinks that exacerbations of disturbance of carbohydrate metabolism are indications of fresh injury to the newly regenerated islands.

This careful quantitative estimation of the insular tissue offers a means of approach to an otherwise impossible diagnosis, and the suggestion should not be neglected despite the fact that serious obstacles have been brought forward against the possibility of estimating the number of islands.

The very careful studies of Bensley[3] by special staining methods have shown that the insular tissue is much more widely distributed throughout the pancreas than had been supposed, and this led him to the opinion that in the estimation of the number of islands the limit of error was as great as 90 per cent.

Nevertheless, until Bensley's methods have been applied to cases such as have been described by Heiberg and Weichselbaum, the hypotheses of these authors cannot be neglected, especially as experimental studies tend to corroborate their views. From this standpoint the histology of the remnant of pancreas in Allen's diabetic dogs illustrates the remarkable regenerative power of the islet tissue in the few animals that were killed when the glycosuria was disappearing. Furthermore, the total disappearance of the insular tissue in animals succumbing to "diabetes gravis" is of significance.

II. Another type of lesion occurring in human diabetes[4] has been described by MacCallum.[5] It is interesting to note that both of MacCallum's cases, and a third one to which he refers, were in children. Sections from the head, middle and tail of the pancreas showed an increase, not only in the number, but also in the size of the individual islands. They averaged .24 x .188 mm. as compared with

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.132 x .156 mm. to .18 x .18 mm. in the normal pancreas. MacCallum concludes that "this change in the islands represents some disturbance of carbohydrate metabolism from extra-pancreatic causes, such as imposed an excessive amount of work on the islands of Langerhans, and that these, in order that they may maintain their control of their own particular link in the process, have undergone the compensatory hypertrophy which has been described." The analogy between the changes in the islands of Langerhans in these cases of MacCallum's and the anatomical changes in the thyroid in hyperthyreosis is striking.

III. Fibrous pancreatitis, both of the interacinar and the interlobular type may be present without diabetes.

This aspect of the subject has been recently reviewed by Major.[3] He points out the well-known fact, which, however, has often been overlooked by observers in their interpretation of the changes in the diabetic pancreas, that extensive fibrosis, diffuse or localized, either of the interacinar or interlobular type may be present in cases in which there is no history of diabetes. It would be of interest, however, to have definite estimations of the carbohydrate tolerance in such cases.

IV. The types of insular diseases which may be present, either in association with the above fibrosis, or in an otherwise normal pancreas, may be divided into two groups, viz.:

a. Hydropic amyloid, pigmentary or fibroid change.

b. Hyaline degeneration.

The division between these types of regressive change has been made, because hyaline degeneration, when it is present, is so striking that it cannot be overlooked. Furthermore, it is a lesion, which when present to any marked degree, is almost invariably associated with glycosuria.

The question of the insular involvement and its relation to diabetes will be discussed after the presentation of the following case:

R. W. F., contractor, white, male, age 57. Medical No. 29,864. Autopsy No. 3814.

***Clinical History.*—The patient was admitted to the medical clinic of The Johns Hopkins Hospital in the service of Dr. L. F. Barker, October 30, 1912. His past history was negative except for syphilis, Neisser infections and the excessive use of alcohol. Eighteen years before admission a life insurance examination had revealed the presence of sugar in the urine, and since that time he had had a typical diabetic history of polydipsia, polyuria and continuous glycosuria. He had not lost weight until the last two weeks before admission. His present illness had begun four days before admis-**

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sion with an acute pain in the region of the right costal margin, nausea, vomiting and diarrhœa.

Physical Examination.—The patient was a well-nourished man with an alcoholic facies. His heart was enlarged and there was a gallop rhythm over the entire precordium. The abdomen was slightly distended and there were signs of an advanced peritonitis with fever and leucocytosis. The urine contained about 1 per cent sugar. There were numerous casts and a heavy cloud of albumin and pus, which often appeared in the form of casts. The Wassermann test was positive; the blood culture negative.

The patient succumbed to peritonitis without operation.

Anatomical Diagnosis.—Primary, 1st: Acute purulent prostatitis; acute cystitis; abscess of the liver with rupture of abscess; general peritonitis; cloudy swelling of the viscera; acute splenic tumor.

Primary, 2d: *Small pancreas with minute fat necroses and extensive progressive (hypertrophy and regeneration) and regressive changes, (hyaline degeneration and atrophy) of the islands of Langerhans.*

Subsidiary.—Chronic mitral and tricuspid endocarditis; chronic fibrous myocarditis, cardiac hypertrophy and slight dilatation; arteriosclerotic scars and healing infarcts of the kidneys; encapsulated tubercle in lung.

The anatomical findings except those in the pancreas have no bearing upon the glycosuria and may therefore be omitted.

Pancreas.—Small and firm. On section a few opaque yellowish points are found in the peri-pancreatic fat. The pancreatic parenchyma does not seem to be atrophied, and there is no marked increase in the fibrous tissue. The organ, aside from its small size and irregular shape, presents no gross abnormalities.

The entire pancreas was carefully dissected and cut into blocks, about 5 cm. in thickness, which included the width of the gland. These were serially numbered, fixed in Zenker's fluid, and subsequently mounted in celloidin.

Microscopically.—The sections throughout the gland show the same general changes. The pancreas is surrounded by fat, which, however, is not present in the gland to any extent. At the periphery of this fatty tissue occasional areas of mononuclear cells, chiefly of the polyblastic series, occur. The fat, in general, is well preserved, but rarely a small area of fat necrosis may be found.

In all of the sections local areas of fibrosis of the gland occur. These occupy only a very small portion of the tissue; the remainder shows no increase in connective tissue. The areas of fibrosis are almost entirely localized in individual pancreatic lobules. The extent of the fibrosis in these lobules is variable. A very marked degree of chronic interacinar pancreatitis sometimes occurs, associated with the usual atrophic acinar changes and prominent ducts. In such lobules the insular tissue does not seem to be affected. In other lobules the fibrosis may be much more extreme, and then the acinar tissue may have entirely disappeared, occasional remnants of the acini appearing as shadows or outlines. All that remains of the lobule is a dense fibrous matrix richly spotted with islands of Langerhans and abnormal ducts.

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The ducts, as a rule, are surrounded by a dense mass of hyaline fibrous tissue. They may be dilated, and they may contain concretions similar to corpora amylacea.

The ducts are frequently dilated, lined with high columnar epithelium with very pale staining protoplasm and basilar nuclei. Not infrequently

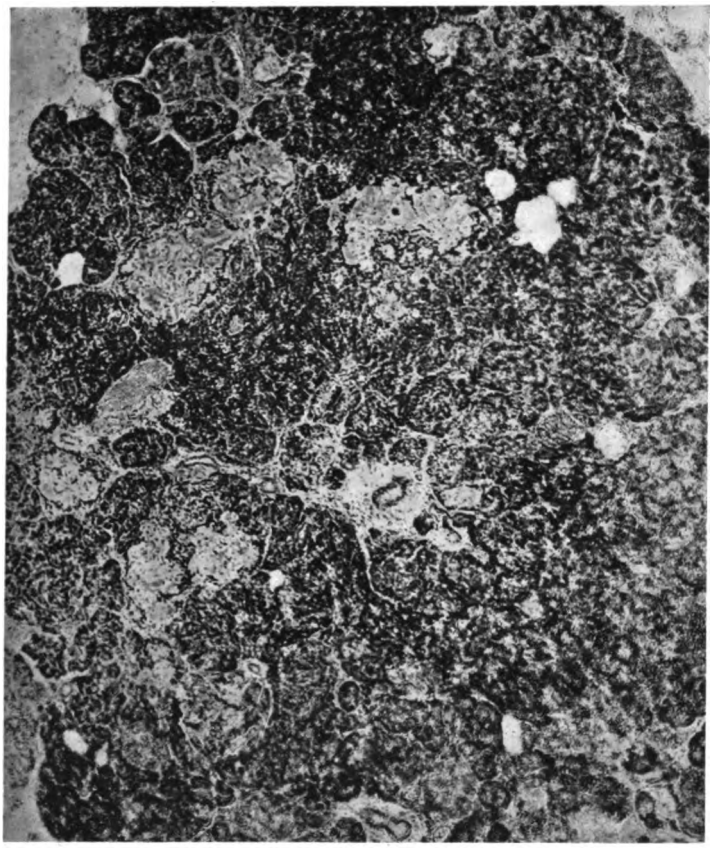

FIG. 1.—A typical field of the pancreas showing numerous hyalinized islands of Langerhans.

the epithelium assumes a peculiar adenomatous formation, such as has been described in detail by Reitmann, Ssobolew, Winternitz, and others.

It must be emphasized that these areas of fibrosis occupy a very small portion of the gland and that elsewhere there is no increase in the interstitial tissue and no extensive acinar or duct changes.

The most marked changes throughout the entire pancreas involve the insular tissue. This is more abundant than normal, but it is not abso-

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lutely uniformly distributed. In the areas of fibrosis, as usual, the islands are extremely prominent. However, they may occur just as frequently in many areas where the pancreas shows no fibrous involvement. On the other hand, relatively large areas of pancreatic tissue occur in which the

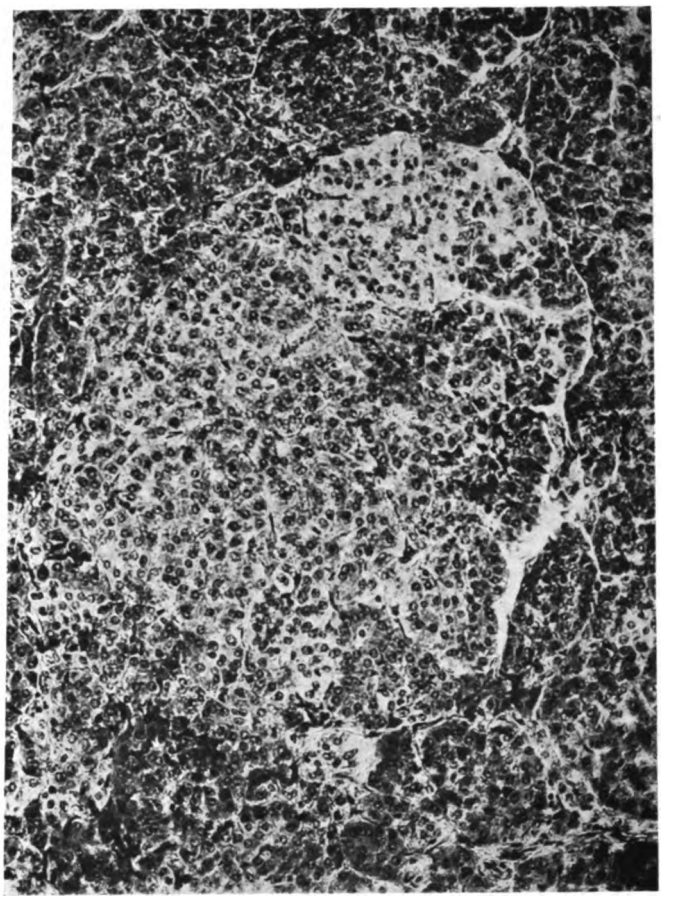

FIG. 2.—A greatly enlarged island of Langerhans, actual size, .35 x .36 mm., with distant variations in staining properties of different groups of cells, indicative either of differences of function or of early degeneration.

islands are considerably less numerous than normal. In general, the number of islands seems to be definitely increased.

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The islands vary markedly in size as may be seen from the following table:

Well preserved islands.....	.35 x .26 to .083 x .066 mm.
Hyaline islands	.42 x .33 to .066 x .03 mm.
As compared to	
Normal islands	.13 x .15 to .18 x .18 mm.

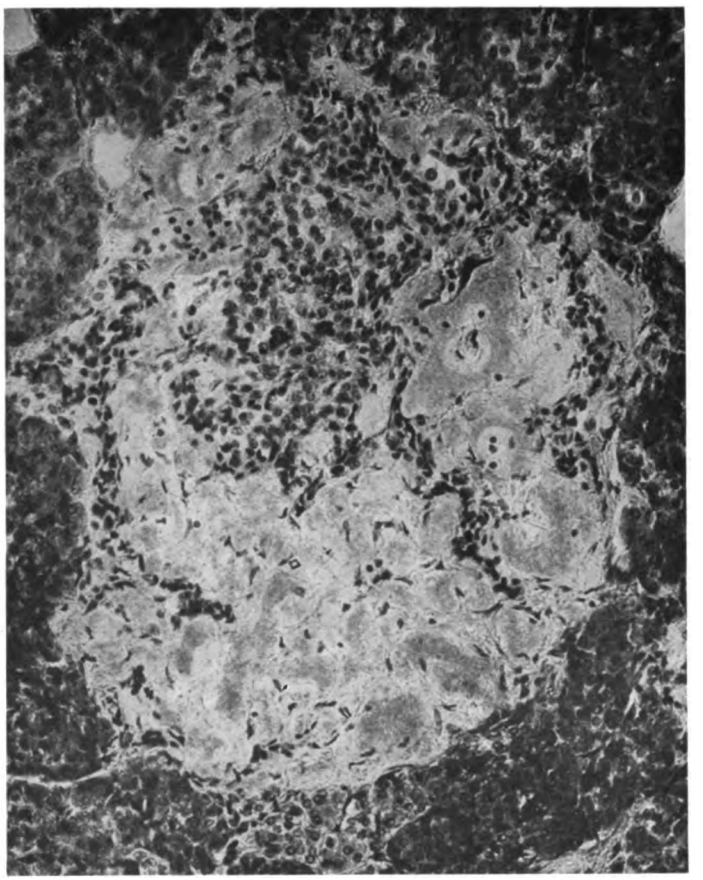

FIG. 3.—A greatly enlarged, almost completely hyalinized, island of Langerhans. Actual size, .42 x .33 mm.

This striking variation in number and size of the islands is only overshadowed by the pathological changes which they are undergoing. By far the greater number are involved in a hyaline degeneration. It is difficult actually to count the percentage of the islands so involved, because the

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hyaline islands are naturally very much more conspicuous than the normal ones. An estimate of several hundred yields the following percentage:

Complete hyalinization	60%
Partial hyalinization	30%
Normal islands	10%

Variation in size occurs in all the islands, both the normal and those

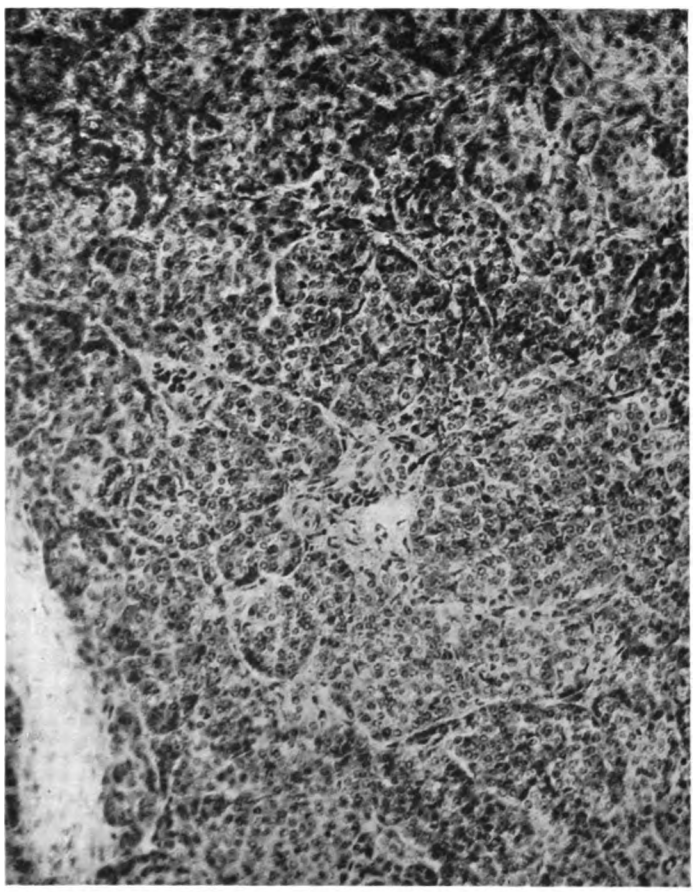

FIG. 4.—A minute, completely hyalinized, island of Langerhans (demonstrated by serial section) probably disappearing.

involved in the degenerative process. Some of the hyaline islands are so large that several of them together occupy the whole field of the microscope. (Zeiss ocular 3, objective AA.) All gradations occur from these large islands to those that appear as very minute, pink-staining balls. A similar variation in size occurs in the partially hyalinized islands. The cells show a disappearance of their nuclei and form tortuous, ribbon-like

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areas of pink-staining material. The connective tissue is only ultimately involved. While the uninvolved islands also vary in size, the majority are small as compared with the freshly hyalinized ones. In many instances their nuclei seem to be more abundant and their cell outlines less distinct. They show characteristic differences in staining properties (see figures), suggestive of early degeneration or differences in function.

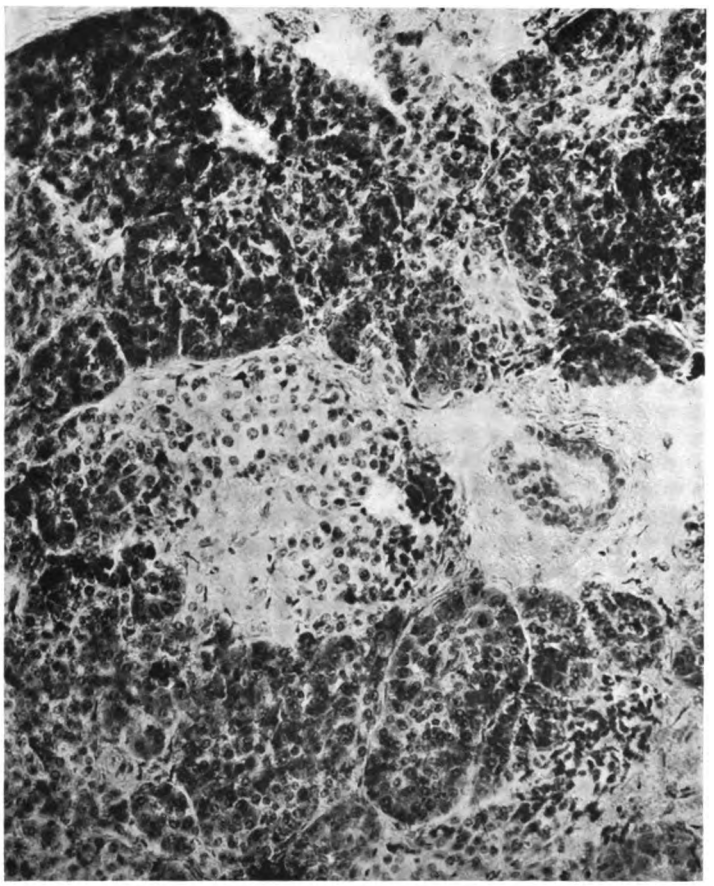

FIG. 5.—A partially hyalinized island of Langerhans.

A synopsis of the microscopic findings in the pancreas of this case would include:

1. Localized areas of fibrosis, associated with duct changes, and atrophy of the acinar tissue. These changes suggest duct occlusion. The areas of fibrosis involve only a small portion of the pancreas.

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2. Numerical increase and wide variations in size of the islands of Langerhans. These are involved in a hyaline degeneration, and a rough estimate yields the following percentage:

Complete hyalinization	**60%**
Partial hyalinization	**30%**
Normal islands	**10%**

3. A new formation of the islands which has occurred more rapidly than the disappearance of the completely degenerated ones. This is indicated by their increase in number and variation in size.

A comparison of the clinical history with the anatomical findings in this case is of interest.

The long duration of the disease (18 years, to the knowledge of the patient) and its relatively mild course, unassociated with exacerbations of sufficient severity to require medical assistance, are at first sight not in harmony with the extensive pancreatic involvement. In the light of more recent investigations, however, the pancreatic changes can be regarded as a manifestation of a continuous process with insular injury followed by insular regeneration occurring over a long period.

Discussion.

1. The more recent experimental evidence is in support of the insular theory of pancreatic diabetes.

2. In the anatomical diagnosis of diabetes, it must be borne in mind that the pancreas forms only one link in the chain that controls carbohydrate metabolism. As a consequence diabetes may occur:

   a. When the pancreas is apparently normal, as, for instance, where there are lesions of the central nervous system or disturbance in certain ductless glands, etc.

3. Where the pancreas is involved, the important lesion is in the insular tissue. This may be altered, (1) quantitatively, by decrease in the number of islands, or by actual increase in the number and size of the islands, or (2) qualitatively. Here no absolute rule can be laid down, as both progressive and regressive changes may occur independently and simultaneously. The remarkable power of the insular tissue to regenerate, as well as the subsequent complete disappearance of the degenerated islands, complicate the anatomical interpretation.

4. The significance of extrainsular pancreatic change is not understood.

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GENERALIZED MILIARY TUBERCULOSIS RESULTING FROM EXTENSION OF A TUBERCULAR PERICARDITIS INTO THE RIGHT AURICLE.

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(From the Department of Pathology of The Johns Hopkins Hospital, Baltimore, and the City Hospitals, Bay View.)

Massive tubercular pericarditis is in itself of relatively frequent occurrence; for the process to extend through the myocardium into a cavity of the heart and act as a portal for the dissemination of a generalized miliary tuberculosis is uncommon and for this reason the case below is reported.

Literature.

Von O. Pertic's [1] review of the literature includes a short discussion of tuberculosis of the heart. He agrees with previous authors in dividing tuberculosis of the myocardium into the following three forms: (a) Large solitary tubercles most common in the region of the right auricle and probably arising from caseous mediastinal glands. (b) Miliary tuberculosis of the myocardium arising as part of a miliary tuberculosis. (c) Diffuse interstitial myocarditis associated with numerous giant cells, but without circumscribed caseous nodules.

A compilation of the cases of the literature is presented in Raviart's [2] more complete study. This has been briefly abstracted in a subsequent report by Beifeld [3].

Raviart points out that tuberculosis of the myocardium is much more frequent than has been supposed. In the reported cases large tubercular nodules of the myocardium occur even more frequently than miliary tubercles. It is probable, however, that the latter are often overlooked. A third form of diffuse tubercular infiltration occurs rarely and a diffuse non-follicular myocardial sclerosis, the rarest form described by the author, involves some difficulty in its etiological classification.

The incidence of the disease in early life is worthy of emphasis. It is as common in the first year as it is in the succeeding four decades. It

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is relatively frequent in the third decade (see case report), but rare after forty.

The seat of predilection is more frequently the left ventricle, although the conglomerate type of tubercle occurs more commonly in the right auricle where it may attain its largest size.

As might be expected, the endocardium acts as a barrier to the progress of the tubercle. Raviart emphasizes this, but cites cases in which the endocardium was ulcerated and gave rise to a focus for the dissemination of the tuberculosis.

The pericardium and lymph glands, more especially those of the mediastinum, are frequently involved.

The path of infection of the myocardium is probably in many cases retrograde through the lymphatics.

A casual glance through the authenticated indices reveals a few other cases such as the one by F. Shedè,[4] and one described by F. Sŭmbera.[5]

The case to be reported is one that occurred in the autopsy service of the City Hospitals during the past year.

A brief abstract of the protocol follows:

Autopsy No. 414. Service No. Phth. 3052. C. B., colored male, age 23 years. Died, February 9, 1915, 11.30 a. m. Autopsy, February 10, 1915, 8 a. m.

The patient was admitted to the Phthisical Hospital in the service of Dr. Gordon Wilson on February 5, 1915. Previously he had been under observation at the Mercy Hospital.

The family and past history were negative. The present illness was believed to have begun in December, 1914, with œdema of the feet, which was at first noticeable only at night. Several weeks later the abdomen became distended and there was dyspnœa on exertion. About this time a slight cough, accompanied by a small amount of sputum, developed. During January, 1915, the patient had several night sweats.

***Physical Examination.*—The head and neck were negative. The pharynx showed slight congestion. The respirations were harsh over both apices. There were signs of fluid over the bases of both lungs. The abdomen was distended with fluid. There was no abdominal tenderness and none of the abdominal viscera was palpable.**

***Heart.*—The absolute cardiac dullness was greatly increased, but no definite margin could be made out. The heart sounds were faint and distant at the apex and slightly more clear at the base. No murmurs were audible. The pulse was 70 to the minute. The blood pressure was 100 systolic, and 70 diastolic.**

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Joints.—In the region of the left sterno-clavicular articulation there was a cold, fluctuating, painless mass about 6 cm. in diameter. The inner end of the left clavicle was unduly movable, and crepitus could be elicited. (No definite history of this swelling could be obtained.)

The temperature was subnormal during the first two days after admission and rose to 100.8° F. on the third day.

The urine was negative. Tubercle bacilli were not demonstrable in the sputum. The Wassermann test was negative. The blood count was normal.

ANATOMICAL DIAGNOSIS. *Tuberculosis of the left sterno-clavicular articulation; tubercular lymphadenitis of the mediastinum; extensive tubercular pericarditis with ultimate extension into the right auricle, and resultant generalized miliary tuberculosis involving all the parenchymatous organs and serous membranes.*

Body.—The body is that of a slightly emaciated colored male, 5 feet 11 inches in length. The pupils are equal and dilated. The mucous membranes are anæmic. The subcutaneous fat is moderate in amount. The recti muscles are well developed. The liver does not extend below the costal margin.

The omentum is practically devoid of fat. The mesenteric lymph glands are either pea-sized and firm, or enlarged, soft and caseous. The peritoneal surfaces are everywhere studded with pearly-gray or yellowish-white nodules, several millimeters in diameter. The peritoneal fluid is increased in amount. The retroperitoneal lymph glands are enlarged and caseous. The appendix and cæcum are involved in old adhesions.

The right pleural cavity is obliterated by old adhesions. There is an increase of fluid in this pleural sac. The left lung lies free in the pleural cavity which contains a moderate amount of fluid.

Pericardium and Heart.—The pericardium is adherent to several masses of enlarged, caseous, mediastinal glands. The pericardial sac is obliterated by an extensive caseous exudate, which unites the visceral and parietal pericardial surfaces. A large chain of caseous lymph glands, extending from the base of the heart to the left sterno-clavicular joint, is particularly prominent.

The heart and pericardium and attached lymph glands are removed with difficulty. This mass is very large and weighs 1120 gm. In the region of the auricle there is a huge tumor-like projection, the surface of which is covered with smaller, pendulous, tumor nodules, which represent adherent glands. On section these present a homogeneous, yellowish, opaque surface.

A similar picture is found on section through the tumor mass overlying the right auricle. This mass measures almost 10 cm. in thickness and is uniform in appearance, except for a V-shaped line which separates its inner third. This line measures only from 2 to 4 mm. in thickness, is slightly reddish-brown in color and resembles muscle. It probably represents the involved dog's ear of the right auricle.

Both ventricles are covered by a densely adherent pericardium with an occasional small, pendulous gland attached to its outer surface. The left

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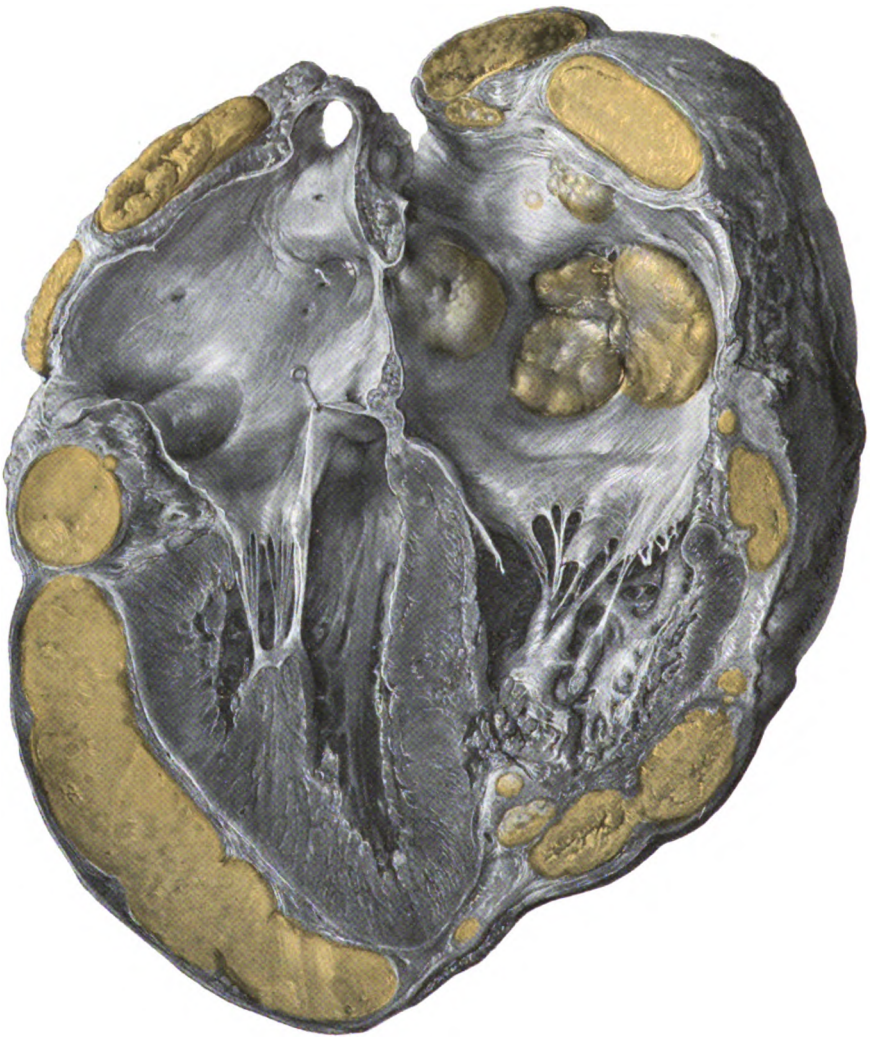
auricle is similar to the right auricle externally, but the thickness of the pericardial mass overlying it is not nearly so great.

The right auricle is slightly dilated. Several mushroom-like tumor



TUBERCULAR PERICARDITIS.

masses project into its cavity. These are irregularly serrated and have a tendency to become umbilicated. They bear a very close resemblance to the nodules of an adenocarcinoma, except that they are slightly more yellowish

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in color and firmer in consistence. They show a tracery of fine vessels beneath the endocardial surface. These masses are covered almost entirely with endocardium and are consequently glistening, except for a few small areas which are dry and granular. These denuded areas represent in their entirety only a few millimeters.

The tricuspid ring measures 12 cm. in circumference and its leaflets are delicate, as are also those of the pulmonary valve.

The wall of the right ventricle presents two definite layers; the outer varies between 5 and 15 mm. in thickness, and consists of a yellowish, caseous substance, similar to that described above; the inner layer is represented by a very translucent, reddish-brown heart muscle, which averages 5 mm. in thickness. In several places the outer, caseous layer impinges upon the inner, muscular layer, and in still other places, isolated caseous nodules are found in the muscular wall.

The left auricle is slightly distended; its endocardium is smooth. Its wall is represented by a delicate muscular coat surrounded by a caseous mass from 1 to 3 cm. in thickness.

The mitral valve is delicate; the mitral ring measures 11 cm. in circumference.

The aorta is not opened. It and the valves appear normal.

The left ventricle is not dilated; its wall is in every respect similar to that of the right ventricle and consists of a caseous and of a muscular layer. The muscular layer measures 13 mm. in the best preserved places. As in the right ventricle, it is impinged upon by the caseous layer, nodules of which are found in the muscle. At times these caseous nodules extend as far as the endocardium.

The accompanying illustration, for which we are indebted to Professor Max Broedel, is taken from the posterior aspect of the heart after the removal of a portion of the wall of the right and left ventricle and septum.

Lungs.—The pleura of the right lung is granular, particularly at the apex. The lung is crepitant throughout. On section, scattered through the entire lung, there are pin-head sized, protruding, grayish-white nodules. The left pleura and lung are similar to the right.

Spleen.—The spleen weighs 450 gm. and measures 16 x 11 x 6 cm. The capsule is wrinkled and gray. On section the pulp is dull red and thickly studded with yellowish-white, cheesy areas, measuring from 3 to 15 mm. in diameter.

Stomach and Duodenum.—The mucosa is pale and presents no abnormalities. The hepatic, cystic and common ducts are patent.

Pancreas.—The pancreas feels firm. On section the parenchyma presents no abnormalities.

Liver.—The liver weighs 1900 gm. and measures 27 x 20 x 11 cm. On section it is reddish-brown in color and the lobulation is distinct. The cut surface is studded with small, yellowish-white areas, 2 to 15 mm. in diameter. The peritoneal surfaces of the liver and gall-bladder are thickly covered with pin-head-sized gray nodules. The gall-bladder contains thick, black bile.

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Kidneys.—**Their combined weight is 240 gm. They are equal in size and measure 8 x 10 x 4 cm. The capsule strips easily, leaving a pale pinkish surface. On section the glomeruli stand out prominently, the pyramids appear unchanged, the striations are distinct. In the cortex there are several small, gray or yellowish nodules, 2 to 5 cm. in diameter. The pelves are small.**

Pelvic Organs.—**The urinary bladder is not distended. The mucosa is pale, and presents no ulceration. The prostate is not enlarged and on section appears normal.**

Intestines.—**The peritoneal surface is everywhere studded with pearly-gray or yellowish-white nodules, several millimeters in diameter. The mucosa is pale and presents no ulceration. The appendix appears normal.**

Neck Organs.—**The thyroid appears normal. The epiglottis and pharynx are not ulcerated.**

Joints.—**The left sterno-clavicular joint is involved in a large caseous mass which is semi-solid in the center. The anterior portion of the sternum and several centimeters of the inner portion of the clavicle are involved in the process.**

Microscopically.—**The pericardial exudate, as well as the sterno-clavicular mass, has undergone a typical coagulation necrosis. The necrotic tissue is in part surrounded by granulation tissue rich in epithelioid and mononuclear cells with occasional giant cells. Typical tubercles occur in all the viscera. They vary somewhat in the relative amount of proliferation and exudation in different localities.**

It is interesting to speculate on the progression of the disease in this instance. The initial portal of entry was not determinable. The two most extensive areas of involvement were the sterno-clavicular joint and the pericardial sac.

As may be seen from the anatomical diagnosis it was believed that the disease of the sterno-clavicular joint was primary and that the process extended partly through a retrograde lymphatic drainage and partly by direct extension into the anterior mediastinum and pericardium. The further extension of the process is, of course, self-evident. The tubercular pericarditis extended into the right auricle and gave rise to a portal of dissemination for the terminal, generalized tuberculosis.

The physiology of the heart itself is interesting. It is difficult to believe that the weakened musculature, handicapped by the extensive pericardial adhesions and the thick casing of caseous material could so nearly sustain the normal function indicated by the clinical report. The œdema of the feet and the dyspnœa were the only apparent symptoms of decompensation.

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ACUTE SUPPURATIVE HYPOPHYSITIS AS A COMPLICATION OF PURULENT SPHENOIDAL SINUSITIS.

By T. R. BOGGS and M. C. WINTERNITZ.

(From the Medical Department and the Department of Pathology of The Johns Hopkins Hospital, Baltimore, Md.)

The recent development in our knowledge of the function of the hypophysis may aid in the recognition of acute inflammatory processes in this organ.

So far as could be determined, no instance of acute inflammation localized in this gland is on record; and for this reason the following interesting case of acute hypophysisitis, arising by extension from a purulent sphenoidal sinusitis and associated with definite signs of an interference with the function of the gland, will be briefly reported.

Clinical History.—The patient, M. S. H., a white woman, 43 years old, was admitted to The Johns Hopkins Hospital June 17, 1915, in the medical service, private ward. She complained of intense stiffness and soreness of the neck muscles, headache, pain back of the eyes and tenderness over the scalp.

Family History.—Unimportant.

Past History.—(From the family physician.) The patient has been robust and active. She has had dysmenorrhœa accompanied by severe frontal headaches every month, requiring morphia; she has had four pregnancies, the last four years ago, during which she had "uremic convulsions." No other sickness of note until the present attack.

Present Illness.—Began May 7 with general aching all over, coryza, sore throat, etc., which lasted a few days. On May 20 she complained of soreness in the right side of the neck. The throat felt full; there was a slight tenderness over both mastoids. Examination of the ears, neck and throat was negative at this time. There was no fever until May 29, when the temperature was 101° F. The pulse was 101. Respirations 20. Blood pressure 135.

Urine.—Albumin and a few casts were present.

On May 30 the patient was improved. The temperature was normal. Several days later there was a sudden attack of pain in the back, of a few days' duration. There was a second attack of pain about the 10th of June. Since then the patient has complained of pain of varying degrees in the right side and back of the neck and over the scalp. X-ray of the sinuses showed the left antrum to be somewhat cloudy. Three X-rays were brought

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by the doctor, but did not show satisfactorily any sinuses except the frontals and antra.

Note by Dr. Thomas, 6/17/15.—The patient is apparently suffering a good deal. The temperature is 103° F. There is pain over the back of the head and neck. The edge of the right optic nerve is distinct. Left optic nerve: The temporal edge is very distinct, the nasal edge is not so distinct. The eyes are sensitive to light. The eye movements are apparently normal. Endeavor to turn the eyes causes pain in the head.

Note by Dr. Boggs, 6/17/15.—The patient can be roused to answer questions, but quickly lapses again. She complains of pain in the head. There is no retraction of the head but stiffness to all movements. There is no paralysis of any muscles.

Chest.—Voluminous; increased resonance to percussion. There are no adventitious sounds of any kind.

Heart.—Not enlarged to percussion. The sounds are distant, the rate increased. The aortic second sound is accentuated; the pulse is somewhat collapsing. The sounds are otherwise clear. Blood pressure 158 (Tycos).

There is no Kernig's sign. The temperature at 3.30 p. m. is 104° F. Leucocytes, 11,600. The blood drawn from a vein this day shows the nitrogen coefficient normal. The blood sugar is 0.243 per cent.

Urine.—The reduction test is atypically positive. Sp. Gr. 1023. There are many casts and a considerable amount of albumin. The acetone and diacetic acid tests are strongly positive. After two slices of bread for supper there was 2½ per cent of glucose in part of the morning urine obtained by catheter (6/18/15).

Note by Dr. Boggs, 6/18/15.—The patient is much worse, more deeply comatose. There is no retraction of the head. The optic nerve heads seem quite normal. Direct and endoscopic examination of the nasal and pharyngeal cavities by Dr. Crowe show that the external orifices of all the sinus ducts are normal in appearance. The maxillary and frontal sinuses are apparently normal on transillumination. There is no evidence of weakness or palsy in the muscles of the eyes, face or head. The neck is stiff as it was yesterday. The temperature is 105.8° F. There is no Kernig's sign. The patient is too sick for an X-ray examination. There is obviously some intracranial inflammatory process. Cerebral abscess (?). Encephalitis (?).

6/19/15.—The patient's temperature has remained high and gradually risen to 107° F. There is deep coma. There is no paralysis of the face or trunk muscles. Opthalmoscopic examination is the same as that of yesterday. There are a few fine râles at the bases of both lungs.

The patient gradually sank and died at 1.30 p. m. The temperature had then risen to 108.5° F.

At no time were there any convulsions, either tonic or clonic. There was no strabismus or ptosis. Immediately after death lumbar puncture showed clear fluid. There were 450 cells per cu. mm.; of these, 25 were white cells, viz., mononuclears 19, polymorphonuclears 6; the rest were red blood cells.

Autopsy No. 4385. Autopsy 2½ hours after death. Dr. Winternitz.

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Anatomical Diagnosis. Primary: ***Purulent sphenoidal sinusitis;*** extension through the sella turcica, involvement of the hypophysis, subacute, hæmorrhagic basilar meningitis, extension along the meninges to the right Sylvian fissure, acute encephalitis (right), cloudy swelling of the viscera, acute splenic tumor. Subsidiary: Bilateral apical pulmonary scars, encapsulated tubercular lymphadenitis (bronchial); bronchopneumonia.

The *body* is that of a well-nourished white woman, 163 cm. in length. Rigor mortis is not present in the extremities. There is only a slight lividity of the back. The pupils are equal and slightly dilated. The abdomen is slightly distended and shows numerous lineæ atrophicæ. The subcutaneous fat is abundant and the abdominal muscles are well developed. The abdominal cavity contains no excess of fluid. The peritoneal surfaces are everywhere smooth and glistening. The abdominal organs are normally disposed.

Thorax.—The pleural cavities are free of excess of fluid and adhesions. A small amount of thymus tissue is found embedded in the adipose tissue of the anterior mediastinum. The pericardial sac contains no excess of fluid. The pericardial surfaces seem normal.

Heart.—Weight, 300 gm. The epicardium contains an abundance of fat; its surface is smooth and glistening. The coronary vessels are not prominent or tortuous. The cavities and valves of the heart present nothing abnormal. The base of the aorta shows a few small slightly elevated yellow patches. The heart muscle, on multiple section, has a uniform reddish-brown color.

Lungs.—The left lung is very small. The lower lobe is particularly small and of a much darker color than the upper lobe. It is non-crepitant throughout its greater portion. The pleural surface is everywhere smooth. There is a minute scar at the apex of the lung. One hilic lymph gland has a calcified nodule within it. The pulmonary vessels are delicate throughout. The bronchi are slightly congested and contain a small amount of frothy serum. On section the upper lobe is pale pinkish-gray in color, the lower lobe of a dark maroon color. No areas of broncho-pneumonia can be definitely made out. The right lung resembles the left in almost every respect. It has the same apical scar, and on section a few small areas of fresh hæmorrhagic broncho-pneumonia are to be made out.

The *spleen* weighs 225 gm. and measures 13 x 8 x 6 cm. Its surface is everywhere smooth and normal in appearance. On section there is an excess of maroon-colored pulp. The Malpighian bodies are small. The trabeculæ are not increased in thickness. The *duodenal mucosa* is slightly bile-stained, otherwise normal in appearance. The *gastric mucosa* is quite pale, except at the fundus, where a few small ecchymoses can be made out. The *bile-ducts* and *pancreatic-ducts* are patent throughout. They join each other just before their common entrance into the duodenum.

The *pancreas* is very large and firm. It has no excess of fibrous tissue. The lobulations are not unduly prominent. On section, the parenchyma has a dull gray color; the islands of Langerhans are made out with difficulty.

The *liver* weighs 1680 gm. and measures 25 x 16 x 8 cm. Its capsule is

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smooth, and on section the lobulation can be made out with difficulty. The parenchyma has a deep reddish-brown color; the periportal areas are pale gray.

The *adrenals* are large, firm and normal in appearance.

The *kidneys* weigh 360 gm. The right kidney measures 12 x 7 x 4.5 cm. Its capsule strips off readily leaving a pale grayish putty-like surface on which stellate vessels can be readily made out. On section, the cortex measures about 6 mm. in thickness. The striations are quite regular. The parenchyma has a yellowish color. The glomeruli are made out with great difficulty. The pyramids are slightly more congested than the cortex. The pelvis is quite normal. The left kidney resembles the right in every respect. The *pelvic organs* present nothing abnormal.

Intestines.—The intestinal muscosa is pale grayish-pink in color throughout.

The head was injected thoroughly with formalin before the removal of the brain.

Brain.—On removal of the scalp a fresh blood extravasation, 6 cm. in diameter, is found in the loose subcutaneous tissue over the frontal bone, otherwise the scalp, calvarium and dura, over the convex surface of the brain, present nothing of importance. The base of the brain is covered with a dark red friable exudate. This is most abundant over the roof of the fourth ventricle and around the optic chiasm. It involves to a lesser degree the roots of the cranial nerves and the cerebral peduncles, and extends through the pia-arachnoid along the right side as far as the Sylvian fissure where it forms an irregular reddish discoloration. This reaches forward as far as the frontal gyrus. The granulation tissue at the base of the brain is spotted here and there with opaque yellowish foci. These are much more prominent along the vessels near the Sylvian fissure, where they become confluent and form mantles for the engorged veins. Smears from these foci show them to contain large numbers of pus cells and staphylococci.

On coronal section of the brain the above-described inflammatory process on the right side of the Sylvian fissure may be seen to extend along the meninges. The entire right half of the substance of the cerebrum has a bluish-pink color, which is most marked near the surface. In the region of the basilar ganglia there are numerous minute areas of softening.

The dura, at the base of the skull, chiefly in the region of the sella turcica, is involved in similar hæmorrhagic granulation tissue.

The hypophysis itself appears as a dark red body. It is more easily seen after the posterior wall of the sella turcica has been elevated. By raising this flap of bone pressure is exerted sufficient to force a small stream of thick creamy pus from the tissue surrounding the hypophysis.

In order to preserve the relationships as well as possible, a large portion of the sphenoid bone with the sinuses, the sella turcica, the hypophysis and the bony septum of the nose are removed together.

The right side of the sphenoidal sinus is filled with a thick pus, which extends along the septum and is present to a less extent in the left side.

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The hypophysis is removed with difficulty from its nest in the bone. This is due to the friability of the gland and to the extensive red granulations which obscure its demarcations. The tissue surrounding it is streaked with pus. Small bits of the anterior lobe, dislocated by the removal, show that the substance of this portion of the gland is of a dark red color.

The remainder of the skull including the ears shows nothing abnormal.

A pure culture of staphylococcus aureus was obtained from the pus of the sphenoid sinus and the heart's blood.

Two sections for microscopic study of the cerebrum were made, one of the entire central portion of the left side and one of a similar portion of the right side of the brain.

The section through the right side shows that the pia-arachnoid on the surface as well as between the convolutions is infiltrated with blood and a varying number of polymorphonuclear leucocytes. In some areas these latter cells predominate and form almost the only constituent of the exudate.

The blood vessels throughout the substance of the brain are prominent. The peri-vasicular tissue spaces are frequently filled with polymorphonuclear leucocytes.

The brain tissue in general seems very little affected. Occasionally small areas of focal mononuclear accumulations occur and polymorphonuclear leucocytes may be found, either in these areas or scattered through the brain tissue. The nerve cells seem somewhat swollen, but no marked changes can be made out in the preparation (hæmatoxylin and eosin).

A similar but much less marked process is found in the section from the left side of the brain.

Hypophysis.—The membranes surrounding the hypophysis show an extensive inflammatory process. The vessels and venous sinuses are frequently occluded by infected thrombi. An exudate consisting of fibrin, serum and polymorphonuclear leucocytes extends from the occluded vessels through the membrane of the hypophysis but, as a rule, does not penetrate the substance of the gland.

The anterior lobe is large and its engorged blood vessels contain an abnormally large number of polymorphonuclear leucocytes. The cells at the periphery of the anterior lobe are not infrequently separated from their basement membrane.

A large V-shaped area, from one-half to one-sixth of the anterior lobe, appears as an infarct. Here the cells are swollen, devoid of nuclei and structureless. The cells directly surrounding this area are slightly involved, but in general the line of demarcation is sharp.

The pars intermedia is not sharply made out in any of the sections. The colloid is normal in amount, but the cells are not well preserved.

In many sections the posterior lobe is swollen and its tissue broken into strands and islands. The irregular clefts separating these have no definite lining cells. Here and there a small bit of posterior-lobe tissue, in which the nuclei are entirely absent, is surrounded by a wall of mononuclear and polymorphonuclear leucocytes. In many of the clefts small masses of necrotic material and polymorphonuclear leucocytes occur.

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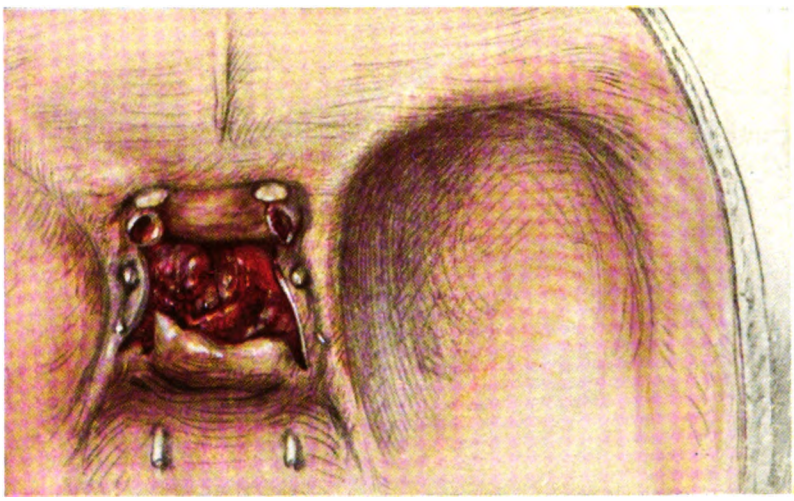

FIG. 1.—Hypophysis from above.

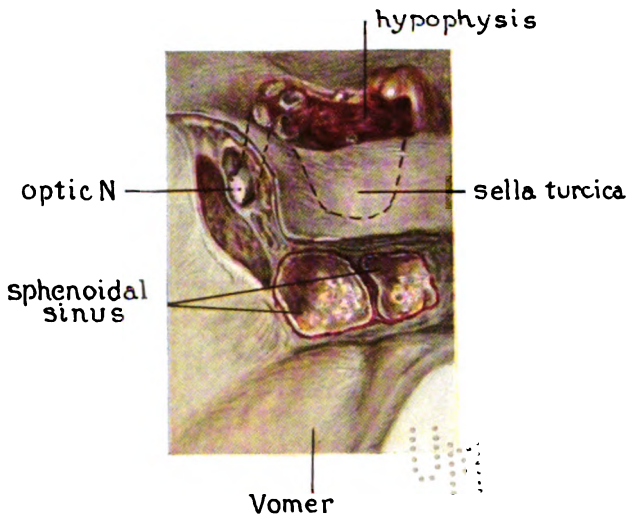

FIG. 2.—Lateral view.
Sphenoidal Sinus.

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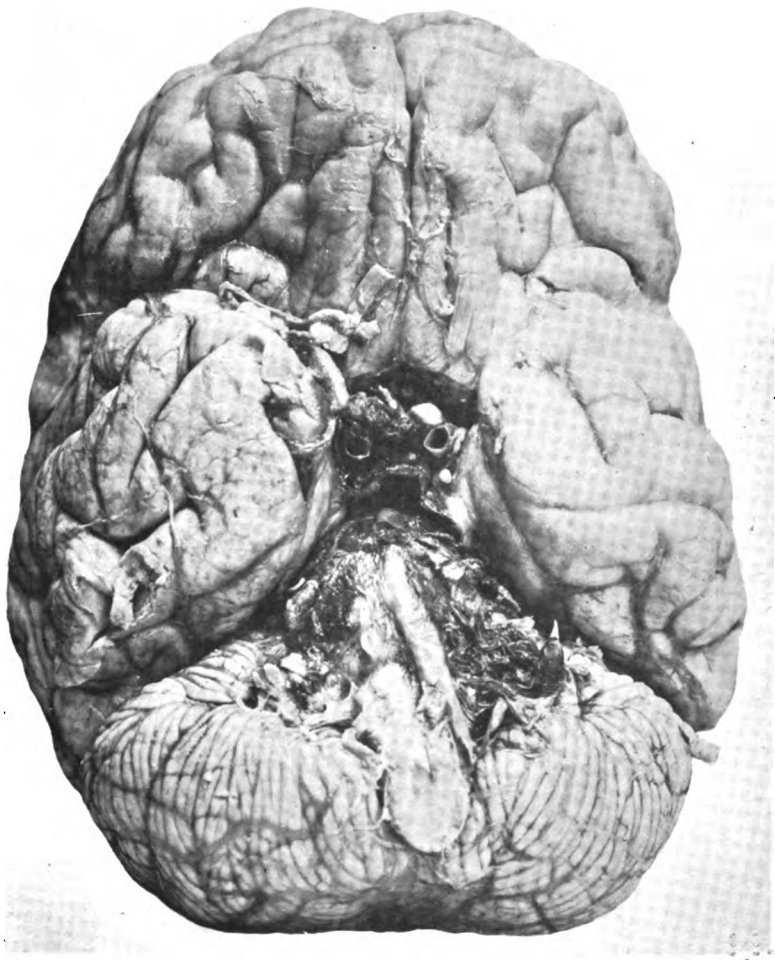

FIG. 3.—Base of Brain.

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The infundibular stalk is swollen and its tissue separated by numerous clefts similar to those in the posterior lobe of the hypophysis. It is surrounded by a wall of acute inflammatory exudate.

Conclusions.

The points of clinical interest are:

1. The entire absence of localizing or neighborhood symptoms in the central nervous system.

2. The presence of hyperglycemia and glycosuria as possible evidence of involvement of the pituitary gland in a person previously not glycosuric and showing signs and symptoms of intracranial inflammation.

3. The normal appearance of the external orifices of the cranial sinuses does not exclude sinusitis of the severest grades.

4. The great importance of a thorough, competent X-ray examination in such cases.

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A CASE OF PULMONARY MONILIASIS IN THE UNITED STATES.

By THOMAS R. BOGGS and M. C. PINCOFFS.

(From the Medical Clinic of the City Hospitals at Bay View and the Department of Pathology of The Johns Hopkins University.)

The patient was a native American housewife, 44 years old. Symptoms of carcinoma of the left breast and an infection of the axilla antedated by 8 months the terminal illness in January, 1915.

A few days after incision into the large axillary abscess the patient suddenly developed a severe cough with profuse expectoration of bloody pus. She died 18 days later, after several severe pulmonary hæmorrhages.

A fine mycelium was found in the expectorated material and from this a pure culture of a yeast-like organism was obtained during the patient's life and also from the autopsy.

This organism on culture developed a characteristic mycelial growth and morphology which seemed to place it in the *Monilia* group. The organism was in all respects morphologically similar to that described by Ashford for tropical sprue.

At autopsy the patient's left lung showed a cavity bounded by the two pleural layers at the apex. This communicated with the lung tissue. There was an extensive pneumonic process characterized by marked proliferation of the alveolar epithelium and the absence of pus cells and fibrin. The intercostal muscles and subcutaneous tissue on the left side of the chest were also involved.

The demonstration of the organism in the tissues was very difficult as they decolorized so readily, but peculiar beaded parallel chains and bizarre stellate and irregular cylindrical forms were found.

The injection of the organism into rabbits by way of the ear vein produced a characteristic disseminated infection with fine grayish-white nodules in the renal cortex, spleen, liver, cardiac and skeletal muscles and the lymph-adenoid tissue of the alimentary canal. The animals died within from 2 to 6 days.

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The organism was recovered from these experimental lesions and demonstrated in sections by the use of special stains.

Intratracheal injection resulted in a pneumonia essentially like that found in the human case. Proliferation of the alveolar epithelium was marked.

Full details of the case and a description of the organism may be found in *The Johns Hopkins Hospital Bulletin,* 1915, XXVI, 407.

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GAUCHER'S DISEASE. A REPORT OF TWO CASES IN INFANCY.*

By J. H. M. KNOX, H. R. WAHL and H. C. SCHMEISSER.

The cases reported occurred in two infants, sisters, who were studied, one at the Thomas Wilson Sanitarium and the other at the Harriet Lane Home.

The first was seen during the summer of 1912, when 9 months of age. She was of Russian-Jewish parentage. There had been 11 children, and none of the others had shown a similar condition. The patient had had no acute symptoms prior to admission, but had never thrived and was considerably emaciated. The abdomen was markedly enlarged owing to the enlargement of the liver and spleen. The latter extended 4½ inches below the costal margin. The skin, particularly about the face and arms, had a brownish pigmentation. The superficial lymph glands were somewhat enlarged. The blood showed a moderate anæmia and an increase in the number of the small mononuclear leucocytes, which was most marked the day before death, when the child was 11 months old.

The most striking changes found at autopsy on gross examination were in the liver and spleen. Both were greatly enlarged. The liver weighed 415 gm. It was yellowish-pink and opaque, with a "putty-like" consistency. The spleen weighed 86 gm. The reddish-brown pulp was mottled with yellowish-pink patches. It had a rubbery consistency. From the sectioned surface of both organs a yellow, frothy, mucoid material, resembling condensed milk, exuded. The adrenals were enlarged.

On microscopical examination nearly all the tissues of the body, particularly the lymph-adenoid tissue, thymus, spleen, liver and adrenals, contained large round, oval or polygonal cells, with a faintly staining cytoplasm filled with vacuoles or small refractile spheres. The nucleus was round or oval and slightly larger than that of a lymphocyte.

The refractile droplets gave the micro-chemical reaction characteristic of lipoid material. In some of the organs these large cells prac-

* A summary of a paper published in *The Johns Hopkins Hospital Bulletin*, January, 1916.

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tically displaced all of the normal tissue. Frequently they were present only in small groups.

While the tissues of the first case were being studied, the mother brought to the Harriet Lane Home another baby, 5 months old. The child presented symptoms practically identical with those of the first case. The blood examination showed changes similar to those in Case 1. The liver and spleen were greatly enlarged. Treatment with radium was not helpful, although following it the number of leucocytes was markedly diminished. The diagnosis was confirmed by the excision of a superficial lymph gland, in which groups of cells characteristic of the condition were found. On examination of the eye-grounds of the second case, cherry-red spots were described in the maculæ similar to those in the amaurotic family idiocy. The patient died after a lingering illness of 10 months. The gross and microscopic post-mortem examination in the second case showed changes practically identical with those found in Case 1, excepting that the process was more intense, and similar cells in large numbers were present in the brain. In both cases the von Pirquet and Wassermann tests were negative.

We believe that this condition is identical with the one first described by Gaucher in 1882. Since this time about 16 cases, confirmed by careful pathological examination, are recorded in the literature. Most of these were in adults, but there is reason to believe that the process may begin in infancy and continue for years unobserved.

The only other case reported in infancy is that of Nieman. The rapidity of the process would seem to be more intense the earlier the age of the patient. The origin of the characteristic cells is uncertain. They seem to arise from endothelial cells of small vessels or from cells of the reticulum. The reason for the remarkable cell picture and the production of lipoid material is still uncertain.

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A FATAL CASE OF MULTIPLE PRIMARY CARCINOMATA.*

By E. D. PLASS.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

This case is one of unusual interest, because it offers a post-mortem confirmation of the clinical cure of a gastric carcinoma by early radical operation, and because it presents a second and a third primary cancer which resulted in death.

It is difficult to eliminate the possibility that a second supposedly new growth occurring in the same individual is not merely a metastasis from the original neoplasm.

The independent genesis of more than one primary malignant epithelial new-growth, together with their occurrence 7 years after a curative operation for adeno-carcinoma of the stomach gives this case exceptional interest.

Case Report.

A Bohemian woman, 43 years old, married, was admitted to The Johns Hopkins Hospital on December 13, 1907. (Medical No. 21,955.)

Complaint.—Burning in stomach and lump in stomach which can be felt at times.

Family History.—Father, aged 57 years, died of cancer of the upper arm from which he had suffered for 18 months. The patient has three children, the youngest 7 years old. The remainder of the history is unimportant.

Present Illness.—Since February, 1907, the patient has noticed a "sense of heaviness" in the stomach after every meal. There never has been any sharp pain or soreness, but frequent eructations. In June, 1907, the distress after eating (distension) had become so obstinate that a physician was called who gave her some relief by medicaments. It was noticed that meat caused more distress than other foods. There was vomiting on only

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* This same case has been utilized briefly by Bloodgood (Jour. Amer. Med. Assoc., 1915, LXIV, 2031), in his article dealing with the cases of gastric carcinoma recorded in the Surgical Pathological Laboratory of The Johns Hopkins Hospital. He reviewed 186 such cases and found only 49, or 26 per cent, operable. Of the 49 cases in which resection was done, only 3 of the patients had remained free from recurrence for 5 years following operation. This case is the same as No. 2 of his report.

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three occasions—the first on November 25, 1907. The vomiting was never prolonged, and each time came on about one hour after eating. The vomitus consisted of food particles, but there were never any black or red masses. During the past four months there has been a progressing weakness and an appreciable loss of weight. A mass has been felt in the upper abdomen for six months.

Physical Examination.—The patient is a thin woman with a slightly pigmented skin. A hard nodular well-defined mass, about 5 cm. in diameter, is easily palpable just above and to the left of the umbilicus. It descends with inspiration and is freely movable, especially toward the right. There is no intrinsic pulsation, no marked tenderness, no muscle spasm, and there are no other masses. Upon inflation the stomach is slightly larger than normal and the mass moves to the right. Occult blood is present in the fæces.

Ewald Test Meal.—40 cc. recovered; one small blood-clot (0.5 cm. in diameter); no free HCl; no lactic acid; total acidity, 13.5 per cent.

A desmoid pill given half an hour after a meal was recovered intact.

BLOOD COUNT.

December 14, 1907:		
R. b. c.	4,800,000	Hgb 80%
W. b. c.	10,000	(P. M. N., 67%; S. M., 25%)
January 1, 1908:		
R. b. c.	3,000,000	Hgb 50%
W. b. c.	8,400	

The temperature varied from normal to 100.5° F.

Diagnosis. Carcinoma of the stomach.

The patient was transferred to the Surgical Service on January 3, 1908. (Surgical No. 21,776.)

Operation.—January 4, 1908; Dr. Miller.

The abdomen was opened by a left rectus incision, 15 cm. long. There was a palpable and visible mass in the anterior wall of the stomach near the pylorus, and there were a few slightly enlarged glands, especially on the lower (greater) curvature. A resection of the pyloric portion of the stomach and a posterior gastro-jejunostomy were made (Billroth 2 operation). The region of the suture was drained. The convalescence was uneventful. The drains were removed on the fourth day and the patient was discharged on the twentieth day.

Description of the Specimen (Surgical Path., No. 8679); Gross.—The specimen consists of the lower portion of the stomach. The mesentery on the lesser curvature is 2.5 cm. long and is slightly infiltrated with inflammatory products. There are several small glands, which feel hard and on section are gray, homogeneous and somewhat soft. They appear inflammatory rather than metastatic. On the greater curvature there is a longer mass of mesentery, which is less infiltrated but contains more glands. One

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of these is quite large (1.0 cm.), rather firm and has a zone of hard white tissue—definitely a cancer metastasis. The tumor is an ulcer which extends around the entire circumference of the pylorus. There is a free margin of healthy stomach tissue, on the stomach side extending about 3.0 cm. and on the pylorus side only 0.5 cm. The ulcer has a smooth round elevated edge, over which normal mucous membrane extends. In some places the mucous membrane dips down and in other places it meets the ulcerated surface at

FIG. 1.—Section through the adeno-carcinoma of the stomach removed 7 years before death.

the top of the rim. The surface of the ulcer is rough, but preserves somewhat the rugæ of the normal mucous membrane. The ulcer consists of a narrow zone of firm tissue extending to the peritoneal coat, which is fixed to the tumor except at the elevated rim. On section the tumor cuts like a cancer. It is of a gray rather homogeneous appearance like a cellular scirrhous cancer.

Microscopical Examination (Dr. Bloodgood).—The ulcer near the center shows hypertrophy of the glands of the stomach with predominating lining

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cells of the mucous type. This probably represents the elevated mucous membrane edge. As the ulcer is approached, the cells of the alveoli change their character. They are smaller, the lining cell is less mucous and there is a great increase of connective tissue between the alveoli of cells. As we approach the center of the ulcer the cells are loose, and in the granulation tissue there is less tendency toward an adenomatous arrangement. The arrangement and morphology of the cells are those of cancer. One gland on the lesser curvature and one on the greater shows probable metastasis.

The patient was readmitted to the hospital February 15, 1915. (Gyn. No. 20,960.)

History of the Interval.—The patient has had no gastro-intestinal symptoms since the operation 7 years ago, and has remained perfectly well until the onset of the present illness.

This began three months ago with morning nausea. At that time the abdomen began to swell and gradually enlarged until it caused shortness of breath. For the past three weeks there has been severe abdominal pain more marked in the lower portion; the appetite has been poor, but there has been no vomiting. The patient has become weaker and has been losing weight for the past three weeks. During this period there has been a profuse vaginal discharge of a sero-purulent, not bloody, character.

Physical Examination.—The chest findings are unimportant, the abdomen is uniformly distended. There is a slight protrusion of the umbilicus and the upper portion of the abdomen gives a high pitched tympanitic note; there is shifting dullness in both flanks. A large tumor mass arises from the pelvis and extends to within about two finger-breadths of the umbilicus. This tumor mass is slightly tender and is quite firmly fixed.

Examination.—The vagina is somewhat relaxed; the cervix is high. There is a large indurated area just within the vaginal orifice under the bladder. The entire anterior vaginal wall is infiltrated. The fundus is in the anterior position and appears about normal in size. The large cystic mass described above is apparently attached to the right broad ligament and bulges into the fornix. The left fornix is soft. There is no œdema, the blood pressure is 130 mm.; the Hgb. 50%.

The temperature showed a daily rise, the pulse remained rapid, the patient gradually failed and died on March 8, 1915.

Autopsy No. 4304, 3 hours after death; Dr. Winternitz.

Anatomical Diagnosis. Primary: Adenocarcinoma of the body of the uterus; metastasis to the regional lymph glands. *Bilateral fibro-cystic adeno-carcinoma of the ovary;* rupture of the cysts with extensive hæmorrhagic extravasation into the peritoneum; anæmia; jaundice; extensive emaciation.

Subsidiary.—Operation: Resection of pylorus *for gastric carcinoma;* posterior gastro-jejunostomy.

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ABSTRACT OF PROTOCOL.

The stomach shows a perfectly healed gastro-jejunostomy and appears normal throughout. There are no evidences of any recurrence of the malignant growth.

The retroperitoneal glands are enlarged and on section are homogeneous, grayish-white in color, with here and there an opaque yellowish spot of necrosis.

The veins around the bladder and vagina are everywhere thrombosed. The bladder shows one small gray nodule in the fundus beneath the mucosa.

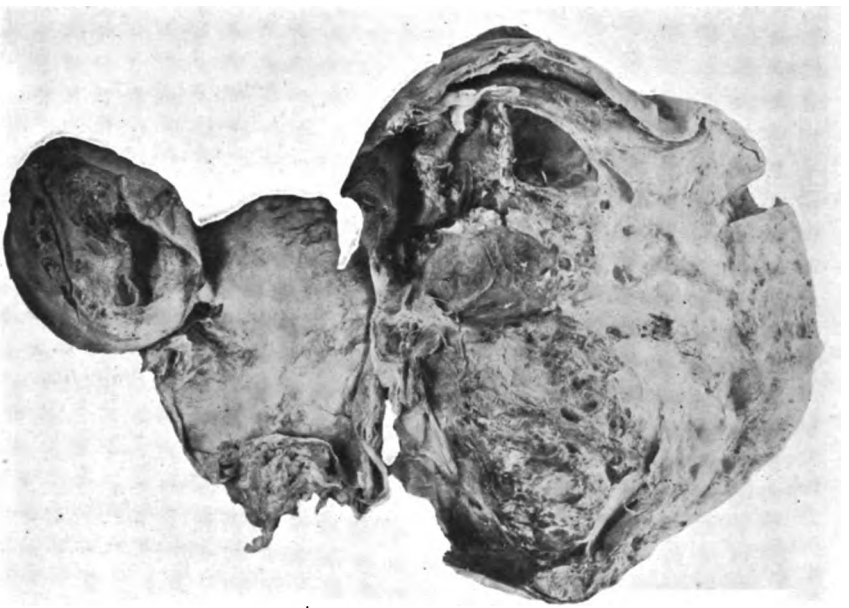

FIG. 2.—Posterior view of the uterus and two ovarian tumors.

The uterus is 9.0 cm. long, 7.0 cm. wide, and the walls are 2.0 cm. thick. The anterior upper surface is studded with yellowish, slightly elevated masses, varying in size up to 1 cm. The cervix appears normal, but there is a yellowish viscous mass protruding from the external os. When the organ is opened through the anterior wall the cavity is seen to be filled with a yellowish friable polypoid mass. The polypoid nature is especially marked near the cervix. The wall is quite homogeneous and yellow in color in the upper portion, whereas near the cervix it is white and irregularly striated with a few small yellow nodules scattered through it.

In the left ovary is noted a cystic mass, 6 x 5 cm. The tube is normal and runs over the upper anterior part of the tumor. The fimbriated extremity

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is patent. The ovarian ligament is short and feels thickened and hard. The round ligament is normal, and there is no apparent induration of the lower part of the broad ligament. The surface of the tumor is smooth and its consistence soft. On section there is a gelatinous capsule with areas of yellowish induration. There is one large and several smaller communicating cyst cavities filled with bloody fluid.

The right ovary measures 16 x 13 x 12 cm., and in general is rather firm. Scattered over the surface there are several cysts, up to 4 cm. in diameter,

FIG. 3.—Section through the endometrium of the uterus showing the adenocarcinoma.

filled with bloody fluid. On section the tumor is reddish in color with irregular areas of yellow tissue. The interior of the cyst cavities is ragged and hæmorrhagic. The tube and round ligament are free and seem normal; the ovarian ligament is short and feels not indurated.

MICROSCOPICAL EXAMINATION (Dr. Elizabeth Hurdon).

Uterus.—The endometrium has been entirely replaced by a papillary glandular growth; irregular epithelial masses invade the musculature in all directions. The epithelial cells filling these alveoli in places show a glandular arrangement, but for the most part form solid nests, many of

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which show central necrosis. The individual cells are fairly uniform in size, but stain irregularly and contain numerous mitotic figures.

Left Ovary.—The small tumor on the left side is made up of large and small alveoli which are irregular in shape and frequently anastomose. These alveoli are filled with closely packed epithelial cells having small deeply-stained, granular nuclei. Here and there the cells are arranged around a small central lumen and are low columnar to cuboidal, but for the most part the cells appear to be spheroidal in shape. The centers of the larger cell

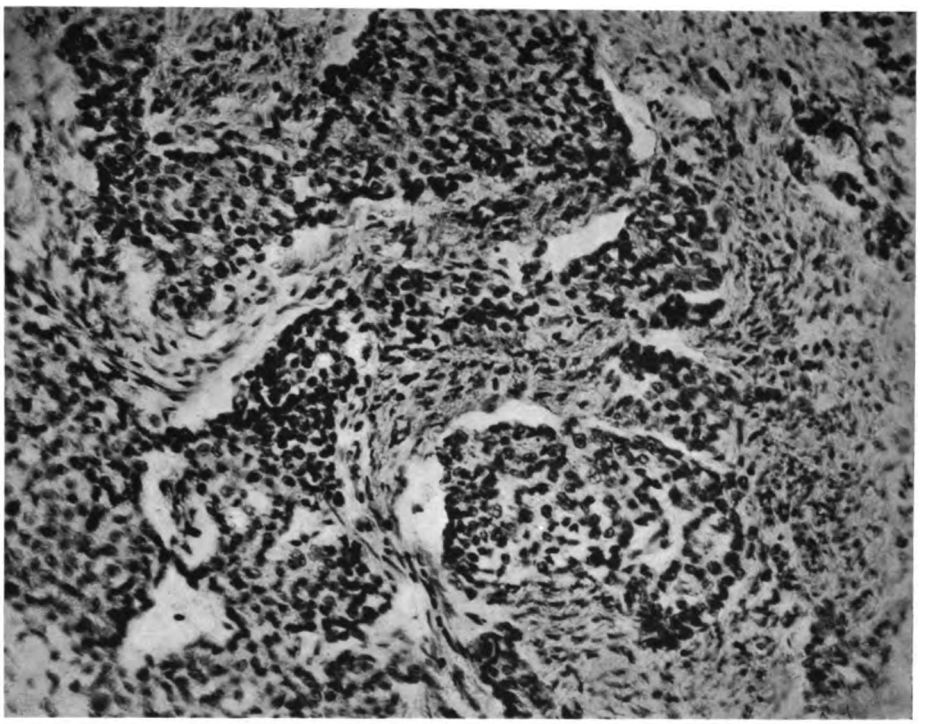

FIG. 4.—Ovarian tumor cells in the peritoneal portion of the uterus.

masses are necrotic, and in many complete liquefaction of the central portion has occurred, giving rise to small cysts which are lined with several layers of epithelium. The abundant stroma consists of an extremely œdematous fibrillated meshwork, containing a moderate number of small spindle-shaped, connective-tissue nuclei. There are a number of plasma cells scattered throughout the stroma.

Right Ovary.—The large tumor of the right ovary is almost completely necrotic, only a small margin of the peripheral portion showing well-preserved tissue. This area presents practically the same structure as that of the left ovarian tumor.

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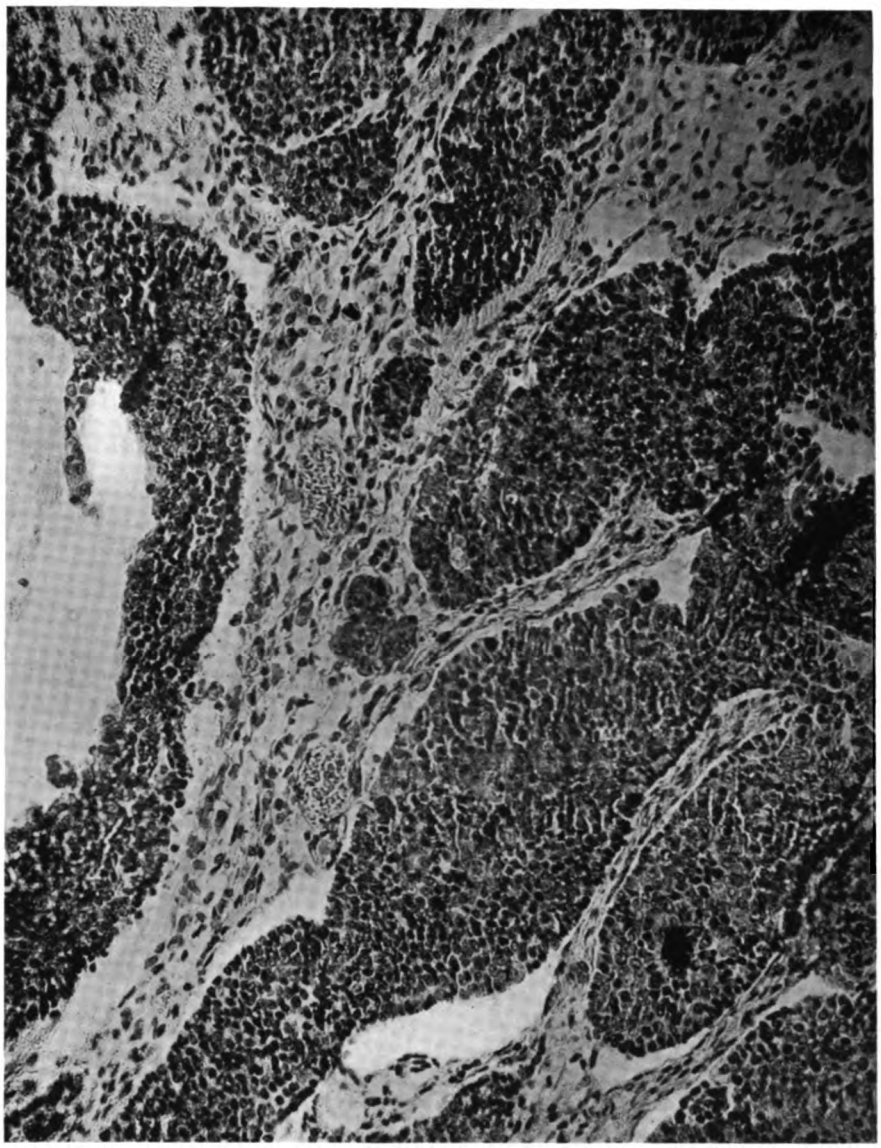

FIG. 5.—Section through the left ovary (high power).

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In the outer muscular layer of the uterus there are several large cell masses resembling those noted in the ovarian tumor. Some of these seem to be enclosed in definite vascular spaces. Similar cell-nests are found in the left utero-ovarian ligament and are probably a direct extension of the ovarian growth.

***Diagnosis.*—Adeno-carcinoma of the uterus. Bilateral ovarian carcinoma.**

Summary.

This case showed a primary adeno-carcinoma of the stomach, with metastasis to two neighboring lymph glands, which was cured by radical operation seven years ago.

Two second primary growths, an adeno-carcinoma of the uterus and bilateral ovarian carcinomata, which apparently bore no relation to the stomach tumor, developed and resulted in the death of the patient.

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CONGENITAL OBLITERATION OF THE BILE-DUCTS.

By JAMES B. HOLMES.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

Congenital obliteration of the bile-ducts is not an extremely rare condition. Over 100 cases have now been reported. The following case is typical in its clinical history and course and unusual only in the anomaly associated with the gross malformation of the ducts. In this it resembles Miller's case. Briefly the history was as follows:

Clinical History.—H. H., a well-developed infant was brought to the Harriet Lane Dispensary, when 7 weeks old, with the complaint that his skin had been yellow from birth. The family history was negative for tuberculosis and syphilis. The birth was normal; the child weighed 8¾ pounds; was breast-fed; the first stools were said to have been copious, loose and green.

When admitted to the Harriet Lane Home at the age of 9 weeks he was well nourished; the skin was uniformly and deeply bile-tinged; the liver and spleen were palpable two fingerbreadths below the costal margin. The blood picture was essentially normal. The von Pirquet and Wassermann tests were negative.

The stool had a slight but definite greenish-yellow tinge; bile-pigments were lacking. The urine stained the napkin yellowish-green, was dark-colored and acid, but not abnormal, save for the presence of bile. A puncture wound in the child's heel bled for many hours and was controlled with difficulty. Two weeks after admission the child vomited blood-stained fluid, and melæna appeared. A week later an ecchymosis appeared over one of the lower ribs, followed by other subcutaneous hæmorrhages. He remained well nourished up to his death at home, at 15 weeks of age.

Abstract of Post-mortem Examination (Autopsy No. 4328).—Rigor mortis is present. All the tissues are bile-stained. The blood is everywhere fluid. The liver is deep purple; the surfaces and cut section are mottled by fine stellate radiations of connective tissue. The intrahepatic bile-ducts do not appear dilated. The anatomical relations of the liver and adjacent organs are normal, as is also the lobulation of the liver. The gall-bladder is represented by a fibrous cord with two dark greenish-black enlargements that contain bile and thick mucus. There are three hepatic ducts. They meet in a common chamber that measures 2 to 3 mm. in diameter and is situated at the level of the junction of the cystic and hepatic ducts. Fine probes can be passed up each hepatic duct to the liver substance. A very

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fine duct leads upward toward the first enlargement in the gall-bladder tract; it represents a partially obliterated cystic duct. A fibrous cord leads from the chamber toward the papilla of Vater; no lumen can be demonstrated in it. The pancreatic duct opens normally, and the pancreas is of normal size and appearance. The hepatic and pancreo-duodenal arteries and the vena cava seem normal. The sympathetic plexus and the foramen of Winslow and its relations are normal.

Microscopically.—The liver shows a marked biliary cirrhosis. The cirrhotic areas contain small collections of lymphoid cells, polyblasts and delicate connective-tissue cells. At the edges this tissue blends almost imperceptibly through gradual transitions into normal liver parenchyma. Normal-looking bile capillaries and ducts occur in the cirrhotic areas and also large sinusoidal spaces filled with coagulated material that resembles serum. Small collections of granular material—bile pigment—lie free in the capillary spaces and between or upon the columns of the liver cells.

Serial sections from the biliary tract show normal pancreatic tissue and ducts, and no evidence of inflammatory reaction in the adjacent structures. The position of the common duct is occupied by loose connective tissue, in which the hepatic vessels and nerves are embedded. The chamber into which the hepatic ducts empty is lined in places with flattened epithelial cells. The cystic duct is impervious for a short distance. Where patent, it is lined with elongated epithelial cells; elsewhere the lumen is occupied by a mass of these cells. The walls of the gall-bladder enlargements, and of the chamber above referred to, consists of more or less tangentially arranged connective-tissue cells. The wall is not unusually thickened and does not appear to be matted to the adjacent structures. The neighboring surfaces of the liver are covered with normal peritoneal lining.

Minor abnormalities, especially those affecting the cystic duct alone, occur with great frequency. Variations in the number and arrangement of the hepatic ducts are not uncommon. The relative size of the various ducts may vary greatly.

Occasionally the constriction or other abnormality leads to atresia or complete obliteration of the gall-bladder, or of one of the biliary ducts. Thomson in 1890, and Benecke in 1907, collected and carefully tabulated in all 74 cases. Since then more than 40 additional cases have appeared.

A careful tabulation of all cases available shows that the utmost variety of lesions are found. Clinically only those cases involving the common duct, or the hepatic ducts (rarer) are of importance. Most published cases are of this type; they alone usually are associated with definite symptoms. In about one-half of the cases in which the common duct is affected, there are other associated lesions, commonly an

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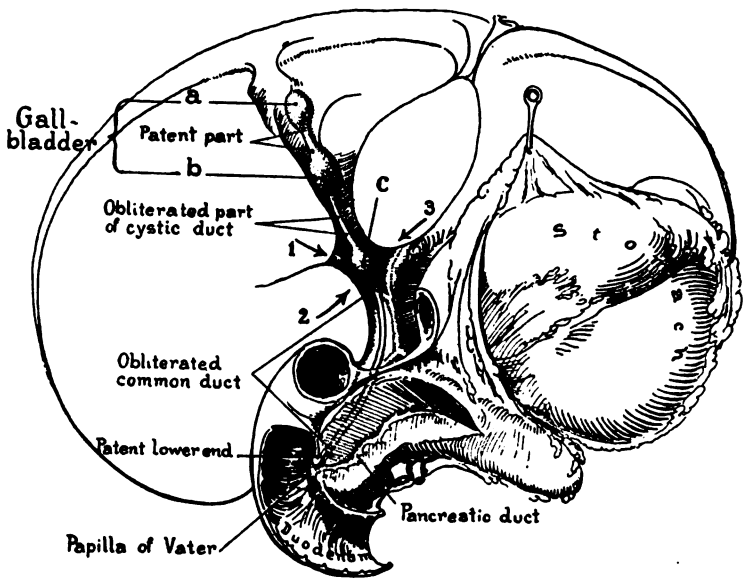
impervious cystic duct or malformation of the hepatic ducts or both. The atresia very rarely may involve the pancreatic duct.

In over 16 per cent of all reported cases of atresia of the bile-ducts, both the cystic and hepatic ducts were essentially normal and communicated with each other.

There is thus established the possibility of surgical relief. Fuller details of this will be given in the completed study, which will shortly be published.



The above drawing by Mr. Max Broedel is a diagrammatic representation of the changes in our case.

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MULTIPLE ABSCESSES OF THE BRAIN IN INFANCY.

By JAMES B. HOLMES.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

Multiple abscesses of the brain in infancy are rare. In the following case it is not possible wholly to exclude multiple tubercles which have undergone puriform softening, though the condition more closely resembles that of multiple pyogenic abscesses. The disease ran its course with the picture of chronic internal hydrocephalus. The history was as follows:

Clinical History.—T. O., a white male infant of 23 months, was brought to the Harriet Lane Home with the complaint "Large Head." The family history was negative. The birth was at full term, non-instrumental; the labor was difficult, but the infant apparently was normal and weighed 9 pounds. He had a severe attack of pertussis at 7 months, without sequelæ. There was never any evidence of trauma or convulsions.

At the age of 16 months he stopped walking and talking, and 2 months later it was noticed that his head had become enlarged. During the next 6 weeks it was thought that the size of the head increased considerably.

On admission, at the age of 23 months, the child was a well-developed, well-nourished boy. He was inattentive; his face expressionless. His head was 52 cm. in circumference, and rather triangular in shape with the apex at the forehead. The forehead bulged, giving the impression that the eyes were sunken. The anterior fontanelle was large and tense; the sagittal suture was ununited, the other sutures firmly united. The superficial veins over the frontal and lateral regions were prominent. The eye-balls were not dislocated; there was no nystagmus or ocular paralysis. The heart, lungs and abdomen seemed normal.

The child used his left arm fairly well; his right arm poorly. The reflexes in both arms and the knee-jerks were exaggerated but equal. There was no spasticity; the Babinski reflex was negative; a fairly sustained ankle-clonus was obtained at times.

The temperature was normal; pulse 140-160; respirations 28 per minute. Urinary examination negative. White blood count 10,000. The X-ray showed "external hydrocephalus" and evidences of pressure on the sella. Lumbar puncture yielded clear fluid, apparently under increased pressure. The Wassermann test on the blood and spinal fluid was negative. The von Pirquet was negative. Attempts at ventricular puncture were unsuc-

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cessful; it was felt that the ventricles were not dilated. A sense of increased resistance on the right side suggested the presence of brain tumor.

The child's condition, temperature, and white-cell count remained unchanged, as did the size of his head. The right hemisphere was then explored; no tumor was found; a good view of the right lateral ventricle was obtained; it was thought to be definitely enlarged; the field was then vacated. The membranes and bone-flap were closed in the usual manner.

After the operation the left arm and leg were flaccid, and by the third night had become spastic. The temperature ranged from 104 degrees to 106° F. The eyes deviated to the left; œdema appeared about the eyes; the leucocyte count rose and the child died. Permission for examination was limited to the brain.

Post-mortem Findings (Autopsy No. 4228).—The left hemisphere is enlarged; the convolutions are wide and flat. The left occipital lobe is relatively soft and the dura is adherent over it. Section through the temporal lobes at the level of the optic chiasm reveals a large abscess in the white matter of the left hemisphere. The wall of the abscess is firm and is apparently composed of dense connective tissue. The abscess contains greenish-yellow purulent material of creamy consistency. The cavity measures 7.5 x 6. 2 x 5.0 cm. The long axis is directed anteriorly. Behind and somewhat mesial to it is a somewhat smaller abscess; a section half-way between the anterior border of the pons and the tip of the occipital lobe passes diametrically across the second abscess. Posterior to this one are three much smaller abscesses. These have less definitely organized walls and the distinction between wall and puriform content is less well marked. The aqueduct of Sylvius is markedly displaced toward the right; the lumen of the left ventricle is completely obliterated by direct pressure; the right ventricle is perhaps a little distended.

Preparations from the contents of the larger cavities and from their walls show no micro-organisms; nor are any found after digestion in antiformin.

Microscopical Notes.—Sections extending through the wall of the cavity and the adjacent brain tissue in various regions show essentially the same features.

The wall of the cavity is lined with masses of mononuclear cells accompanied by a very few polymorphonuclear leucocytes. The former contain globules of lipoid substances; the latter are typical "pus cells." The wall itself is formed of dense fibrous tissue. The cells are long and slender, with uniform glassy protoplasm; the nuclei are slender and similar to those of ordinary connective-tissue cells. Groups of mononuclear cells like those in the exudate are found as inclusions; certain of them stain faintly with Sudan III. Adjacent to the fibrous capsule and blending with it is a zone of blood vessels. They are relatively numerous and large; lymphatic spaces are seen near the larger vessels. Beyond this vascular tissue the compressed degenerated cerebral tissue can be seen. This has a tendency to fall into strands that represent single cylinders or groups of axis cylinders.

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Fine droplets of lipoid substances stained with Sudan III are seen everywhere. The larger droplets are phagocytized. Beautiful examples of cerebral granular cells are seen everywhere. The evidences of degeneration diminish as the pia is approached. This is slightly thickened. Its capillaries are somewhat enlarged. There is no obvious cellular infiltration of the pia.

Taken as a whole, the sections are remarkable for the unusual development and sharp definition of the fibrous capsule or zone of connective-tissue reaction and for the prominence and great variety of the cerebral granular cells.

The microscopical study yields no evidence that the lesions are tuberculous. It seems very probable that they are multiple pyogenic abscesses. As such, they are exceedingly rare at this age.

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GASTRIC CARCINOMA IN A WOMAN OF TWENTY-SIX YEARS.

By R. G. HUSSEY, M. D.

(From the Department of Pathology, the City Hospitals, Baltimore, Md.)

The occurrence of primary gastric carcinoma between the ages of 20 and 30, as collected by various authors, varies between .87 per cent and 3.4 per cent, the average being 3.32 per cent. In some instances the figures quoted are based on both clinical and autopsy findings, in others on clinical evidence only. The percentage is usually higher in the latter instances. In a collection of 2604 fatal cases of gastric carcinoma Fenwick reports 2.5 per cent under the age of 30. In 882 cases gathered from various London hospitals, based on clinical findings only, 3.4 per cent. Welch, in a collection of 2038 cases, finds 2.8 per cent; Reiche, in his Hamburg statistics, 0.9 per cent.

Six cases between the first and tenth and 16 between the tenth and twentieth years have been reported. The diagnosis of many of these is, to say the least, open to question. Fenwick, Osler, and others, think it very probable that cases of lympho-sarcoma and hypertrophic stenosis of the pylorus were mistaken for carcinoma.

Most authorities agree that gastric carcinoma occurs with equal frequency in the sexes. However, Fenwick, in a collection of 25 cases occurring before the age of 30, found the condition strikingly more prevalent in the male, a ratio of 5: 1. All of the 6 cases reported by Osler and McCrae were in the male.

Primary gastric carcinoma in the young usually has a sudden onset and runs a rapid course, the mean duration being about 3 months. There is no evidence that gastric carcinoma in the young shows any predilection for site, or peculiarities of metastasis.

The following case of gastric carcinoma in a woman of 26 years is of interest:

C. B., a white woman, age 26 years, was admitted to the medical ward of the City Hospitals in the service of Dr. Thomas R. Boggs, June 10, 1915, complaining of "stomach trouble and vomiting."

The family history is unimportant, as is also the personal history until the present illness. She has had no gastric symptoms except occasional

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attacks of pyrosis, easily relieved by bicarbonate of soda. Her appetite has always been good. For the past 10 years she has indulged moderately in alcoholic beverages. She was married 10 years ago and divorced the following year. There were no pregnancies and no menstrual disturbances. The patient has always worked hard (seasonal occupation in local canning houses and general housework).

The onset of the present illness was about 4 months previous to her admission, with repeated attacks of nausea and vomiting. The vomiting

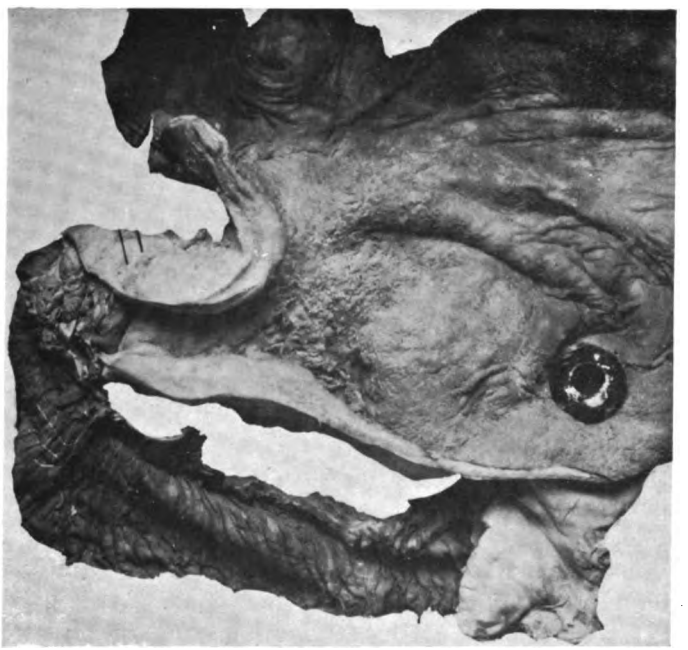

FIG. 1.—The stomach has been opened along the anterior surface between the greater and lesser curvatures. The thickened wall at the pylorus gradually approaches the normal towards the cardia; the duodenum is not implicated. The gastro-jejunal fistula is held open by a Murphy button. A section of a large gelatinous gland is seen on the lesser curvatures near the pylorus.

occurred at first about half an hour after eating, but gradually this interval became shorter; there has been no blood and no pain associated with it. For two months she has noticed a hard lump in her upper abdomen. There has been progressive loss of appetite, weakness and emaciation.

The physical examination shows an extremely emaciated young white woman apparently suffering no acute pain. The abdomen is retracted, the walls are thin, there are no operative scars, no dulness in the flanks. The

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hepatic dulness begins at the fourth rib and extends to the costal margin. The spleen and kidneys are not palpable. There is a sausage-shaped mass, smooth in outline, situated midway between the ensiform and umbilicus. It is freely movable, not tender, and descends on inspiration.

The blood Wassermann is negative. The hæmoglobin is 98 per cent (Sahli). The white blood count is 9400.

The systolic blood pressure is 70. The clinical impression is "pyloric obstruction, probably carcinoma of stomach; and starvation."

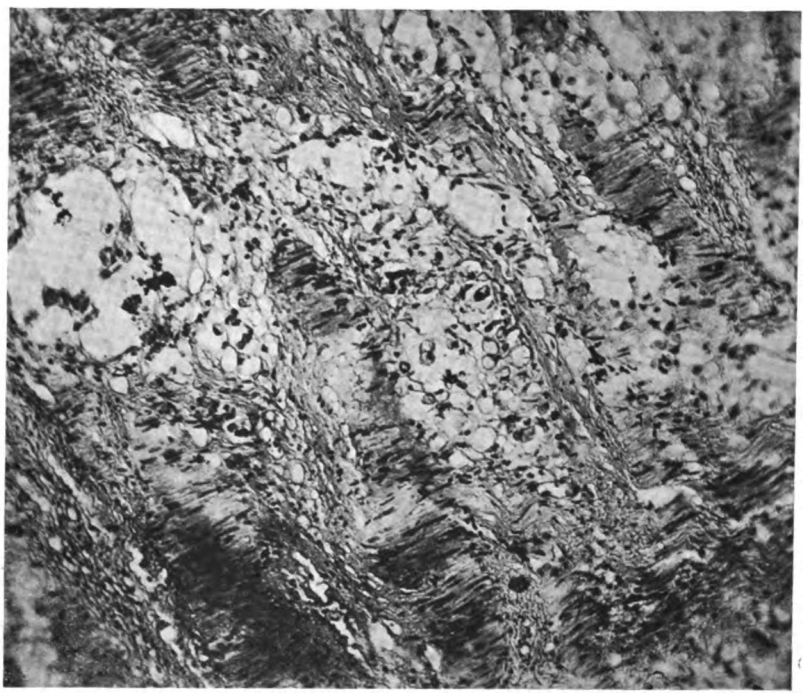

FIG. 2.—Microphotograph of section through the submucosa (low power).

During the first days at the hospital the patient was given nutrient enemas which were retained. She vomited whenever any fluid was given by mouth; she was generally uncomfortable, but complained of no definite pains. Dr. Shipley, Chief of the Surgical Clinic, saw her and advised laparotomy, which was carried out on the sixth day after admission.

When the abdomen was opened, the stomach was found to be involved in an extensive malignant process; an anterior gastro-jejunostomy was done and the patient was returned to the ward in very good condition. She died 11 days after the operation.

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Autopsy, July 4, 1915 (in brief).—The body is that of an extremely emaciated young white woman, 150 cm. in length. There is a recent laparotomy incision which is held together by catgut sutures. The subcutaneous fat is very scanty, the pectoral and abdominal muscles are atrophied. After separation of adhesions about the incision the peritoneal surfaces are seen to be everywhere dull grey in color and covered with a granular reddish exudate. The liver, stomach and surrounding tissues are matted together. A portion of the small gut is attached to the anterior

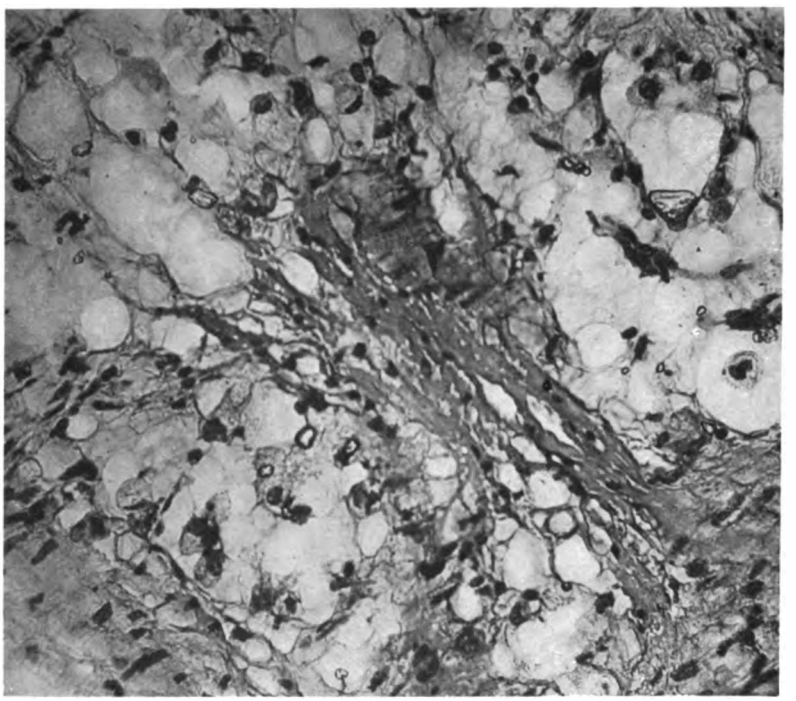

FIG. 3.—In many of the spaces tumor cells can be seen (high-power picture of Figure 2).

wall of the stomach by silk sutures. The pylorus is firm and this increased consistence extends along the lesser curvature towards the cardia. The glands adjacent to both curvatures are enlarged and unusually firm; one large softer gland at the lesser curvature on section has a thick homogeneous gelatinous appearance (Fig. 1). The gastro-jejunal fistula is held open by a Murphy button. The duodenal mucosa shows nothing abnormal. The pyloric orifice is so constricted that a 1 mm. probe cannot be passed unless considerable force is exerted. The stomach contains a small amount

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of semi-solid yellowish material; its cavity is considerably reduced, the thickness of the wall at the pylorus is 15 mm. and decreases gradually towards the cardia, where it is fairly thin; the rugæ towards the cardia are well marked. The mucous membrane is intact except for an oval area 2 cm. in its long diameter; this is situated on the posterior wall about 4 cm. from the pylorus and extends from the lesser to the greater curvature. Here the mucosa is rough and has a yellowish opaque appearance. On section the stomach wall is firm in consistence, translucent and pearly-gray in color. The œsophagus presents nothing remarkable.

Anatomical Diagnosis.—Primary: *Carcinoma (colloid) of the stomach;* pyloric stenosis; metastasis to the regional lymph glands. Emaciation. Anæmia.

Subsidiary.—Chronic cholecystitis with stone.

The microscopical examination of sections taken from various parts of the stomach show that the mucous membrane has undergone extensive digestion. From the area on the posterior wall near the pylorus the submucosa shows accumulations of mononuclear cells. The submucosa and muscular coats are extensively infiltrated by the tumor (Fig. 2). The tumor cells vary in shape and size, but for the most part are cubical or cylindrical; they have large vesicular nuclei and their cytoplasm is frequently vacuolated; these vacuoles may be very large and give the cell a signet-ring-like appearance. Furthermore, many such cells may be grouped together, forming nests of a tumor which contain few cells and a fine trabecular tracery of cell membrane in a large cyst-like cavity.

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SUBDIAPHRAGMATIC ABSCESS WITH RUPTURE INTO THE PERITONEAL CAVITY FOLLOWING INDUCED PNEUMOTHORAX FOR PULMONARY HÆMORRHAGE.

By R. G. HUSSEY, M. D.

(*From the Department of Pathology, the City Hospitals, Bay View, Baltimore.*)

Medical literature during the past few years contains a wealth of material discussing the many aspects of the use of compression of the lung by induced pneumothorax. Indications and contraindications for the treatment, and the complications arising during its use are the chief subjects of discussion. The following case, which came to autopsy from the Tuberculosis Clinic of the City Hospitals at Bay View, is of interest from its clinical as well as its anatomical aspect, particularly so, because in the extensive literature on the subject there is a decided lack of data giving autopsy findings in unsuccessful cases. In the case under discussion the procedure cannot be considered unsuccessful, because it controlled the pulmonary hæmorrhage which was the indication for its application.

W. L., white, male, age 31, was admitted to the Tuberculosis Clinic of the City Hospitals in the service of Dr. Gordon Wilson on May 18, 1915, complaining of "spitting blood."

The family history is interesting. The father of the patient has had tuberculosis for many years, and during early childhood the patient was exposed to the infection.

Past History.—The patient has never had any definite illness save for some of the ordinary diseases of childhood, which were not associated with sequelæ. For about 20 years he has been troubled with a cough which has been particularly noticeable during the past 10 years. The story of his cough is characteristic; a morning cough which at first was dry and hacking and later productive of thin mucous expectoration; worse in the winter; easily aggravated by "colds" and not yielding very promptly to ordinary treatment. He also has complained of definite pains throughout his right chest and shoulder, and has had night sweats. His habits have been fairly regular; while not a total abstainer, he has never drunk or smoked to excess. He has worked regularly as a baker since he was 16 years of age, and was married 3 years ago. His maximal weight was

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180 pounds, 4 years ago; usually he weighs about 160 pounds. He was not weighed on admission, but it was apparent that he had lost considerably.

The onset of the present illness was about 18 months before admission, when he had to stop work on account of a severe pain in his right side; he applied to one of the local dispensaries for treatment and at the end of a week he returned to his work, although he did not feel entirely well. The cough and expectoration became particularly troublesome, and he felt generally uncomfortable, and again gave up work in a few weeks. From this time until his admission to the hospital his condition varied; he worked at intervals, but gradually and steadily declined. Cough, expectoration, together with loss of weight and strength, were the principal features. About 5 months before admission fluid was removed from his right chest by paracentesis. About one month before admission he noticed blood in his sputum.

The physical examination showed a somewhat emaciated white male with rapid respirations, 32 to the minute; these were interrupted occasionally by cough and expectoration of a blood-streaked muco-purulent sputum. The radial pulse was regular in frequency and rhythm; the vessel wall was not thickened; the pulse was 112 to the minute; the blood pressure was 112/80. There was no general or local glandular enlargement. The relative cardiac dulness was within normal limits; the point of maximum impulse was in the fifth interspace, 9 cm. from the mid-sternal line.

The lower right chest showed a markedly retarded movement. Percussion of the right chest showed moderate impairment from the apex to the fourth rib, definite impairment from the fourth rib to the base, in front; definite impairment from the angle of the scapula to the base, behind. Auscultation over the front showed intensified breath sounds with fine moist râles above the fourth rib; distant to almost absent breath sounds, somewhat tubular in quality, with coarse râles from the fourth rib to the base; these same changes were heard in the back from the angle of the scapula to the base. The left chest was clear on percussion and auscultation.

Tubercle bacilli were demonstrated in the sputum.

Impression.—Cavity in the right lower lobe with thickened pleura; infiltration of the upper and middle lobes.

During the first few weeks in the hospital there was no particular change in the patient's condition. Cough with blood-streaked sputum continued, and there was a daily rise of temperature to 100.2 ° F.; the pulse ranged from 110 to 130.

One month after admission the patient had a frank pulmonary hæmorrhage of about 250 cc.; partial compression of the right lung was thought advisable to control the bleeding and 300 cc. of nitrogen gas were injected by the Forlanini method. The manometer reading at the beginning was -5, -12; at the end, -2, -6. There were no untoward symptoms during or following the treatment; after a few hours there was some displacement of the heart to the left. The bleeding apparently was controlled. No change in the temperature or the pulse rate was noticed.

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Two weeks later there was another hæmorrhage of about 250 cc. At this time the manometer readings were -5, -13, and 300 cc. of nitrogen gas were injected with a final reading of -1, -6. Again the bleeding was controlled. Further manometer readings were made at intervals during the next 10 days, and on 3 occasions further compression was made. The manometer readings were never above -1. Following these subsequent injections the patient complained of no discomfort, although there was considerable gradual displacement of the heart to the left. The last injection was given July 10, 250 cc. of gas being injected with a final reading of -2, -7. About 4 hours afterward the patient complained of considerable pain and difficulty in breathing, and showed signs of shock. Attempts to reduce the thoracic pressure and stimulants were without effect, and the patient died about 4 hours later.

The *autopsy* done the following morning showed the body of a well-developed but emaciated young white man, 160 cm. in length. There was nothing remarkable externally. When the abdomen was opened, the liver was found markedly displaced downward, the upper surface being almost at a level with the costal margin. The diaphragm was felt immediately above, but one could not pass the hand between it and the upper surface of the liver on account of adhesions. The first of these were easily broken, but about a finger's length back they were dense and firm. In the right peritoneal cavity there was a small amount of thick yellowish-white semi-fluid material. Very slight manipulation of the abdominal viscera increased the amount of this fluid.

When the thoracic cavity was opened, the heart was found displaced to the left, the right border being at the left sternal margin. The upper third of the right thoracic cavity was empty, the parietal pleura was smooth and glistening; the lower two-thirds contained the lung. The two upper lobes were compressed, non-crepitant, and fitted like a cap over the lower lobe, which was adherent to the chest wall by dense adhesions. The left pleural cavity showed nothing remarkable. The abdominal and thoracic viscera were removed *en masse*. The lower lobe of the right lung was soft and fluctuant. The middle third of the base was involved in dense adhesions, which glued the pleura, diaphragm, and upper surface of the liver together. At the lower posterior border of the lower lobe there was a sinus which led into a huge cavity occupying almost the entire lobe. This cavity was surrounded above, in front and behind, by lung tissue which was non-crepitant and studded with many soft, yellowish-white areas. The sinus apparently connected the cavity in the lower lobe of the right lung with a semi-fluid mass between the posterior third of the upper surface of the liver and the diaphragm; this in its turn communicated with the peritoneal cavity. In passing a probe into the right bronchus there was an apparent narrowing of the lumen of the bronchus to the lower lobe. On section the upper two lobes of the right lung showed atelectasis; the cavity, which occupied almost the entire lower lobe, contained a large amount of thick, dirty, yellowish, semi-fluid material. The left lung presented nothing abnormal.

Anatomical Diagnosis.—Primary: (1) Chronic ulcerative pulmonary

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tuberculosis of the right lower lobe. Chronic adhesive pleurisy. (2) Operation: Artificial pneumothorax (right) with compression of upper and middle lobes. (3) Sinus formation connecting cavity in right lower lobe with subphrenic abscess; rupture of abscess into the peritoneal cavity. Subsidiary.—Chronic perihepatitis with adhesions to diaphragm and pleura in middle third.

The unusual finding of a tubercular cavity of the lung communicating with a subdiaphragmatic abscess which ultimately ruptured into the peritoneal cavity, permits the assumption that the compression played a rôle in bringing about the condition.

This case is furthermore of interest as it adds an illustration of compression of the lung, associated with partial obliteration of the pleura.

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HEART BLOCK CAUSED BY GUMMA OF THE SEPTUM.

By E. W. BRIDGMAN and H. C. SCHMEISSER.

(From the Departments of Medicine and Pathology of The Johns Hopkins University and Hospital, Baltimore, Md.)

We are fortunate in being able to record an example of heart block in which the complete clinical and pathological findings can be compared. The case presents several points of interest which, both from their rarity and from their possible bearing on the normal cardiac physiology, merit consideration.

T. C., colored, unmarried, laborer, 28 years of age, was admitted to the medical service of The Johns Hopkins Hospital on May 13, 1915, with the complaint of "An Injury to the Head." His family history is unimportant. The patient has always enjoyed good health. His tonsils were removed 15 years ago, and he has suffered occasionally from tooth-ache; otherwise a careful history gives no further information of importance. He denies venereal infection, and his genito-urinary as well as his cardio-respiratory history is not remarkable. Daily, he has taken a drink of gin and smoked half a dozen cigarettes.

For the past two months the patient has had dizzy spells, in which he has often fallen and injured himself. According to his mother, "He says that a ball of pain rises up in the top of his chest and hurts him bad. He wants to get it out of his chest, but nothing don't seem to do no good. Then he gets vertigo in the head and can't stand up." On April 21, less than a month before admission, he fell off of a wagon and struck his head on the brick pavement. He was able to go back to the store and load his wagon, apparently suffering no symptoms, although the present illness is dated from this accident. For some time the patient has been treated by a physician, who said that his pulse was the slowest that he had ever felt, "sometimes only 15 to the minute." The patient has received some sort of medicine which seems to have precipitated the attacks of vertigo, for his mother says that after he had taken some of the black medicine "he most always had a dizzy spell." For the past ten days there has been a good deal of hiccough.

On admission a physical examination was made by Dr. Bayne-Jones, who noted the following features: The patient was breathing comfortably, but was hiccoughing frequently. Although he was somewhat confused and not completely oriented, he gave a fairly correct account of himself. The scalp showed superficial scars, with one pigmented scar over an exostosis in the right frontal region. There was slight weakness of the right facial muscles

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with definite ptosis of the right eyelid. The eye-grounds were normal. The respirations, 20 to the minute and characterized by an expiratory grunt, were suggestively Cheyne-Stokes in type. There was slight impairment at the right apex with some suppression of breath sounds, and in the left axilla there were a few squeaky râles at times.

The apex of the heart was seen and felt in the fifth left interspace, 11 cm. from the mid-line. It was a strong, heaving impulse, beating 16 times per minute. Between each of these "ventricular" contractions occurred numerous wavy impulses over a broad area in the fourth and fifth left interspaces. The veins of the neck were distended, and in the right jugular bulb about 85 pulsations were visible per minute. The relative cardiac dullness extended 12.5 cm. to the left and 4.5 cm. to the right of the mid-line, and was continuous with a slight retromanubrial dullness. At the apex two sets of sounds were audible; the one loud, and probably of ventricular origin, with a fair degree of regularity, that was broken by premature beats suggestively extrasystolic in character; the other softer, always regular, and probably caused by auricular contractions. There was a systolic blow that was well transmitted. The pulses were synchronous with the strong cardiac sounds—18 to 20 per minute, and regular, except for an occasional paired beat. The pulse was somewhat collapsing in quality, and the blood pressure was 130 mm. The vessel walls were slightly thickened.

To percussion, the liver extended 1 cm. below the costal margin, but the edge was not palpable. The abdominal examination disclosed nothing further of interest. There were several punched out scars on the penis. Except for some thickening and bowing of the tibiæ the extremities were not remarkable. The reflexes were normal.

The red blood count was 4,800,000. The white cells were 13,000, and the hæmoglobin estimate was 92 per cent (Sahli). The differential count was unimportant. The 24-hour specimen of urine, over 750 cc., had a specific gravity of 1.020, and showed a large amount of albumin and a few coarsely granular casts. The phenolphthalein excretion was 41 per cent in 2 hours.

Wassermann tests done by Drs. Miller and Evans on the blood and cerebrospinal fluid obtained on admission, and subsequently at post-mortem, were all later reported negative. The post-mortem spinal fluid, however, showed 25 mononuclear cells to the cubic millimeter and gave a faintly positive Ross-Jones test. An intra-vitam blood culture was negative.

Roentgenographic examination by Dr. Baetjer showed a thick, deep sella and some infiltration and clouding of the lower right chest.

During the patient's stay in the hospital the respirations varied from 18 to 26 per minute. The temperature rose from 98 degrees on admission to 102 degrees F. at the time of death. The pulse rate was fairly steady, at 20 to the minute.

After the entrance examination the patient was put to bed and given a restricted cardiac diet with limited fluid intake. Eighty grains of potassium iodide and 45 grains of diuretin were ordered daily.

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On the day after admission, Dr. Clough noted that the patient's pulse rate was 16 to the minute and regular. There were numerous small waves in the veins of the neck, and also large waves that were synchronous with the strong apex beats. The apex of the heart was visible in the fifth left interspace beating 16 times per minute. There were numerous small waves over the precordium. A systolic thrill was palpable. The relative cardiac dulness extended about 4 cm. to the right of the median sternal line in the fourth interspace, and 2 cm. to the left of the nipple line.

About the middle of the following night, Dr. Bayne-Jones saw the patient who had just passed through a "convulsion," which the nurse described as "a stiffening out of his whole body." There had been no clonic contraction, and no evidence of unilateral spasm. The patient was breathing heavily with the Cheyne-Stokes type—vigorous dyspnœa alternating with 10 seconds of apnœa. The pulse was more rapid, rising to 40 per minute in dyspnœa, but slowing markedly in apnœa. The auricular sounds were about 114 per minute. Atropin 1/150 gr. was given hypodermatically with no appreciable effect.

At 8 o'clock the next morning Dr. Bayne-Jones again saw the patient, who had almost ceased breathing. Camphorated oil had been administered with some improvement. The Cheyne-Stokes respiration was marked. The pulse was irregular with rapid and slow rates alternating. Some pulsus bigeminus and trigeminus was noted.

After two hours the patient was seen by Dr. Janeway on ward rounds. At this time the apex beats were very irregular, sometimes they were 60 per minute, whereas there were other periods during which there were 5 seconds between succeeding beats. The relative cardiac dullness was as noted previously. The strong beats were seen at the apex with wavy impulses between. The veins of the neck were engorged, and pulsated synchronously both with the strong and weak beats. The ventricular sounds at the apex were booming, with rapid, fainter, auricular sounds in between. A systolic murmur was audible. The lungs were not remarkable on a brief examination. The liver edge was palpable just below the costal margin. There was a positive Oppenheim on the right.

The patient was sent to the heart station on the afternoon of his admission. In addition to the other findings, it was noted that, on close examination, there was a very rapid pulsation of the somewhat distended neck veins, suggesting, from the frequency and apparent regularity, an auricular flutter. This opinion was strengthened by the observation of the apex, where similar, very rapid oscillations were observed of over 200 per minute. These regular, well-marked waves in the neck were interspaced at fairly equal intervals, by strong, flopping waves that undoubtedly were of ventricular origin, and which were practically synchronous with the radial beats. Auscultation was very interesting, in that there was clearly heard, at the apex and over the lower pre-

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cordium, a sound corresponding to each of the little venous undulations. These sounds were so spaced that they suggested split sounds occurring regularly 120 times per minute. Their intensity was noteworthy. This observation was later confirmed by numerous observers. The very loud ventricular sounds reverberated markedly, and between the normally paired ventricular sounds was a coarse systolic murmur. It is interesting that later, as the heart weakened, the auricular sounds decreased markedly, and the day before death the split character was lost and only one soft sound was audible with every two venous waves.

On admission numerous simultaneous tracings were taken with very clear results. Unfortunately the tracings were complicated by the convulsive movements of hiccoughing, which during observation came with every ventricular contraction. However, because of the unusual sharpness of the double auricular sounds the electrophonograms are shown in Figures 1 and 2. The general increase of intensity of A_2 from one ventricular systole to another is noted. The period of ventricular systole is the normal time, .31 second, while the time interval between the two phases of split auricular sound equals .13 second.

On the following day further simultaneous apex, venous, and electrocardiographic tracings in the three derivations were taken. They show a complete heart block with a ventricular rate of 15, and an auricular rate of 130 per minute. The P waves are at times diphasic with a slight tendency to be split. They are always upright. P_2 is very high. There is no increase of the height of the P waves between the ventricular systoles, as is so often seen in cases of heart block. The R waves are not remarkable. There are no Q waves, but well marked S waves are seen in all derivations. The T waves progressively decrease from D_1 to inversion in D_3. The ventricular complexes are constant in the particular derivation.

Following each P wave, there appear double waves on the apex and venous tracings. The first of these, evidently due to auricular contraction, follows the P wave at the expected interval and is, necessarily, on both the apex and venous tracings, the result of auricular contraction. These (here designated A_1) waves are about synchronous on the apex and venous tracing, just as the A wave of the normal venous tracing appears at practically the same time as does the auricular wave on the apex tracing. The waves marked A_2, however, are not so easily explained, but possibly originate as tension phenomena resulting from the closure of the atrioventricular valves following the auricular systoles

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which had opened these valves. It is true, of course, that the *C* wave of the normal venous pulse is partly a delayed transmitted blood wave through the auricular blood from the tension of the tricuspid valve leaflets at the beginning of the ventricular systole, while the part played by the transmitted carotid pulsation is delayed also by the presphygmic period. In other words, the normal *C* wave occurs about one-tenth of a second after the onset of the anacrotic limb of the apex cardiogram. In the same way, in this individual, the A_2 wave in the venous tracing occurs about one-tenth of a second after the A_2 wave on the apex trac-

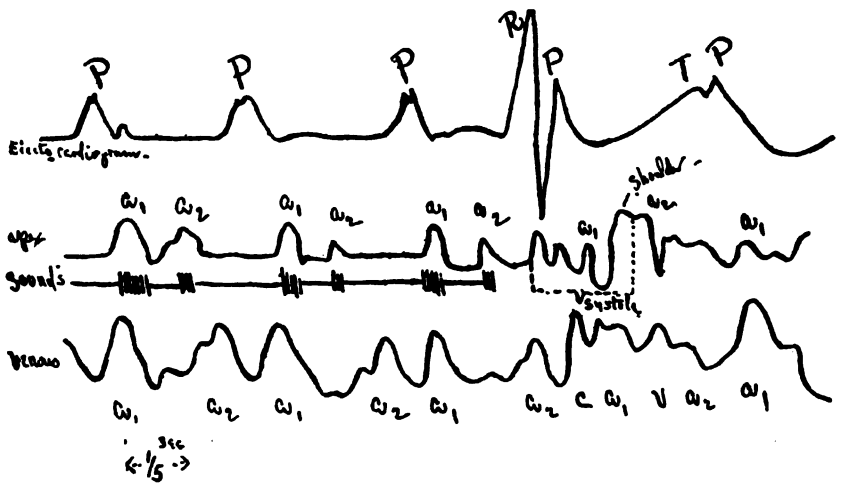

FIG. 3.—A semi-diagrammatic representation of synchronous points on the apex, venous, electrocardiographic and electrophonographic tracings.

A_2 on the venous comes about 1/10 second later than the A_2 on the apex tracing. In the same way the *C* wave on the venous comes about 1/10 second after the onset of the ventricular systole as marked on the apex cardiogram.

There is no actual excitation curve on the electrocardiogram to suggest cause for the A_2 waves in cardiac muscle activity.

Possibly the atrio-ventricular valve closure after auricular systole accounts for the A_2 waves and venous tracings.

ing. Regarding the cause as intimately connected with tension phenomena in the atrioventricular valves, one could rather easily explain the delayed transmission time in the venous pulse.

The sound tracing shows a normal period of ventricular systole .31 second, with an intense systolic murmur. The split auricular sounds are evident, the first of which occurs soon after the onset of auricular

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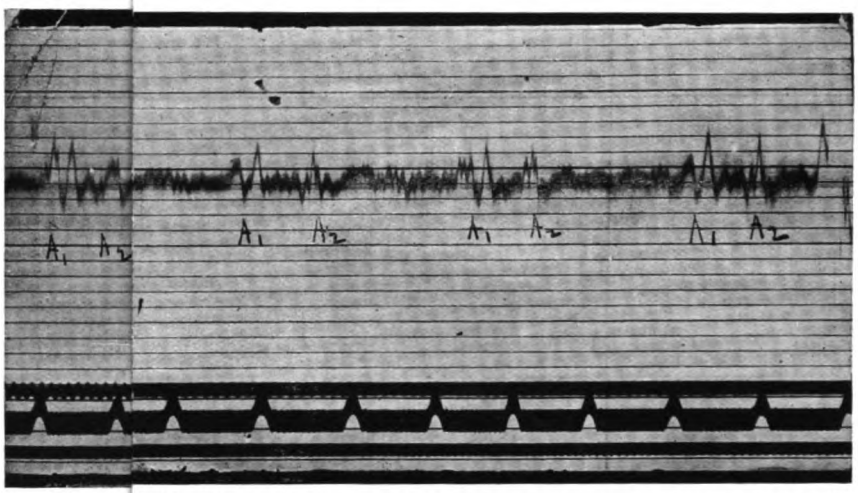
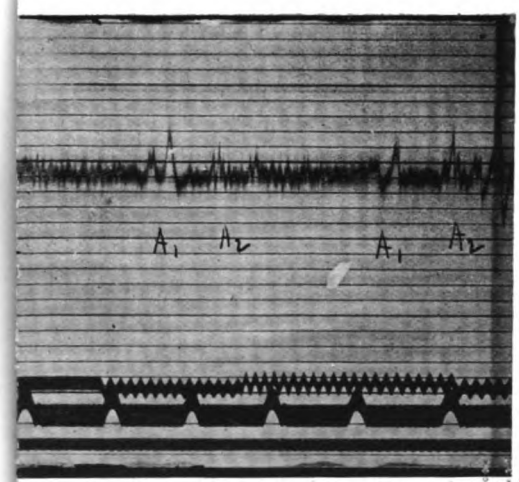


FIG. 1.—Ele regularity in the appearance of the auricular beats. A hiccough



und. The systolic murmur is clearly marked
second. Both are normal time intervals.

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contraction, and the second beginning .13 second later, that is near the onset of the second auricular wave of the apex.

In Figure 3 appears a semi-diagrammatic sketch of the different tracings to show their relationship. The original tracings appear elsewhere.

The following is an abstract of the Autopsy Protocol (Autopsy No. 4358):

The *body* is that of a medium-sized, muscular, colored male, 167 cm. in length. The left pupil is larger than the right. There is a small puckered scar behind the corona of the glans penis. There are several non-pigmented irregular scars, about 4 cm. in diameter, on the right shin. Numerous smaller pigmented scars are scattered over both shins. Both lower legs are arched forward (saber shins), but the surfaces of the bones are smooth.

Peritoneal Cavity.—The convex surface of the left lobe of the liver is adherent to the diaphragm; otherwise the peritoneal cavity presents nothing abnormal.

Thoracic Cavity.—The right pleural cavity is obliterated by fibrous adhesions; otherwise the serous membranes in the thoracic cavity present no abnormalities.

Heart.—Weight, 420 gm. It is slightly but uniformly enlarged. The epicardial surface is smooth and glistening. The epicardial vessels and fat seem normal. The right auricle is slightly dilated; otherwise it presents no gross abnormalities. The tricuspid ring measures 11 cm. in circumference. A nodular, opaque, yellow mass occupies the upper portion of the interventricular septum. This mass has a smooth endothelial surface; it projects into the right ventricle, involves the posterior cusp of the tricuspid valve, and measures 4.5 x 3 x 1.5 cm. The remaining cusps of the tricuspid valve are not involved; the chordæ tendineæ present nothing abnormal; the cavity of the right ventricle is somewhat dilated; the wall is slightly thickened (4 to 6 mm.), and the mural endocardium is smooth throughout. The pulmonary orifice, valves and artery are apparently normal. The left auricle presents no gross abnormalities; the mitral ring measures 10 cm. in circumference; the mitral valve and chordæ tendineæ are delicate. The left ventricle is not dilated and its walls measure 12 cm. in thickness. The mass in the right ventricle extends through the septum and has a similar appearance on the left side of the heart in the position of the membranous septum.

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It projects 0.8 cm. from the endocardial surface, impinges upon the aortic orifice and measures 4 x 2 cm. The endocardium of the left ventricle and the aortic valves are delicate; a dry friable clot partly fills the sinus of Valsalva of the posterior aortic valve. The base of the aorta is remarkably free from pathological changes.

The *pancreas* is small, firm and cuts with resistance. On section, there seems to be an increase in the interlobular connective tissue.

The *liver* measures 26 x 19 x 7 cm. and weighs 1500 gm. The capsule, especially over the superior surface of the left lobe where it was adherent to the diaphragm, is thickened and milky in appearance. The dome of the left lobe shows several depressed puckered scars; two of the larger ones, 4 and 8 cm. long, respectively, cross each other at right angles. On section, these scars may be seen to extend into the hepatic parenchyma for a considerable distance, distorting the architecture of the liver in their vicinity. They may contain small yellowish-white opaque nodules several millimeters in diameter, and similar nodules occur elsewhere in the liver parenchyma, where they are also surrounded by a variable thickness of translucent bluish-gray scar tissue. Elsewhere the liver shows the typical changes of chronic passive congestion.

The *testes* are smaller and firmer than normal, and on section are profusely streaked with dense, bluish-white translucent scars.

The remaining abdominal viscera present a mild grade of chronic passive congestion.

Microscopically.—Between the lobules of the pancreas there is a fibrosis rich in mononuclear cells.

The opaque nodules in the liver show a central area of coagulative necrosis surrounded by an epithelioid small, round cell and an occasional giant cell. These in their turn are surrounded by a hyaline fibrous connective-tissue wall. The testes show an atrophic and degenerative change of the seminiferous tubules and a marked increase in intertubular connective tissue.

Section of the scar of the penis shows an absence of the skin papillæ overlying a dense fibrous mass.

In view of the change in the liver, testes and bones of the lower extremities it seems justifiable to regard the mass involving the septum of the heart as a tertiary syphilitic, gummatous lesion, even though the Wassermann test was negative. It is well known that gummata may localize in just this portion of the heart, although they are rare.

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Conclusion.

The case then is clearly one of *heart block* resulting from gumma of the septum. Clinically, it is of interest to note the negative Wassermann, and the double waves in the apex and venous tracings, which

Gumma of the Interventricular Septum of the Heart Involving the Bundle of His.

were associated with double sounds in the electrophonogram, but with only one wave in the electrocardiogram. The double auricular sounds were clearly audible, the first being associated with auricular contraction and the second being, possibly, a tension phenomenon developing at the atrioventricular orifices.

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ANALYSIS OF AUTOPSY RECORDS.

It has become increasingly evident that the autopsy records were reaching a stage at which they would have to be carefully analyzed to be of the greatest use. The cooperation of the Prudential Life Insurance Company through its statistician, Mr. Frederick L. Hoffman, was obtained for the analysis of these records.

In the fall of 1914 a conference between Mr. Hoffman and a committee from the hospital agreed on the following scheme of approaching the problem.

The 5000 autopsy records are to be condensed to a single volume, each autopsy to be recorded on a single line as represented in the attached chart, No. I. To facilitate this a system of abbreviations and a code for the localization of lesions were adopted and furnished to several members of the medical staff of the Prudential Life Insurance Company, who have been actively engaged in filling in the Anatomical Diagnoses on the adopted blank.

Volume I is to include the records of 5000 autopsies and will be completed early in 1917.

In order that this work could be carried out, duplicate volumes of the protocols were necessary. Twenty-five hundred autopsies had to be copied and many of the earlier ones were in manuscript form.

At the same time it was planned to represent each autopsy on an individual card. (See Chart No. II.)

Blocks 1 and 4 of this card are being filled in at the Statistical Department of the Prudential Life Insurance Company. Many cards belonging to Block 1 are incomplete, and means will later have to be devised for completing them.

In order to fill in Blocks 2 and 3 it will be necessary to revise the arrangement of most of the clinical and anatomical diagnoses. Block 5 will be filled in by a representative of the Prudential Life Insurance Company.

We wish to take this opportunity of expressing our indebtedness and appreciation to Mr. Frederick L. Hoffman, the physicians of the Prudential Life Insurance Company, and the company itself for assistance in this investigation.

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CHART I.

THE JOHNS HOPKINS HOSPITAL AUTOPSY INVESTIGATION—1890-1915.

	Clinical Diagnosis.	Cardio-Vascular.	Respiratory.	Gastro-Intestinal.	Genito-Urinary.	Hæmato-poietic.	Skeletal and Nervous.	Ductless Glands.	Miscellaneous.	General Body Conditions.	Remarks.
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										
No. Race Sex Age	R C										

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CHART II.

CLASS.
Free.....
Pay.....

THE JOHNS HOPKINS HOSPITAL.
AUTOPSY RECORD INVESTIGATION.

1. Autopsy No.....Hospital No.....Service Division.....
Name of Patient..... Date of Death.....
Age.....Sex.....Race.....Occupation.....

2. Clinical Diagnosis: Primary Cause of Death.....
.....
Contributory Cause or Causes.....
.....
.....

3. Anatomical Diagnosis: Primary.....
.....
.....
.....
Subsidiary.....
.....
.....

4. Anatomical Measurements: Height.....Cm. Weight.....Kilos.
Heart: Weight.....Grm. Thickness of Left Ventricle Wall.....
Liver: " ..... " Width.....Cm. Length.....Cm. Thickness.....Cm.
Spleen: " ..... " " ..... " " ..... " " ..... "
Kidney: " ..... " " ..... " " ..... " " ..... "

5. Board of Health Record: Certified Cause of Death.....
Classified Cause of Death.....
Clinical Diagnosis of Death Confirmed..... Not Confirmed.....

THE CITY HOSPITALS, BAY VIEW.
TABLE SHOWING PERCENTAGE OF AUTOPSIES.

Year.	Number of Autopsies.
1908	84
1909	75
1910	88
1911	92
1912	72

Service.	1913. Number of Deaths.	1913. Percent. of Autopsies.	1914. Number of Deaths.	1914. Percent. of Autopsies.	1915. Number of Deaths.	1915. Per cent. of Autopsies.
Medical.....	227	39	273	38	274	45
Surgical.....	55	44	77	43	69	39
Phthisical	261	16	239	33	242	52.8
Insane	88	3.4	86	20	67	30

Total Number of Deaths. 1913-1915.	Total Number of Autopsies. 1913-1915.	Percent. of Autopsies. 1913-1915.
631	153	25.8
675	228	33.8
652	297	45.4

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THE JOHNS HOPKINS HOSPITAL.

TABLE SHOWING PERCENTAGE OF AUTOPSIES.

(This report is taken from records that are not entirely complete and is therefore subject to correction.)

	Med. Service.		Surg. Service.		Gyn. Service.		Obst. Service.		Ped. Service		Psy. Service.	
	Number of Deaths.	Percent. of Autopsies.	Number of Deaths.	Percent. of Autopsies.	Number of Deaths.	Percent. of Autopsies.	Number of Deaths.	Percent. of Autopsies.	Number of Deaths.	Percent. of Autopsies.	Number of Deaths.	Percent. of Autopsies.
1911.....	122	74.5	136	33.0	25	36.0	10	40.0	....	....	..	....
1912.....	151	70.8	116	31.8	27	25.8	11	81.8	....	....	..	....
1913.....	108	85.1	107	34.5	22	36.3	4	17.5	92	57.6	5	100.0
1914.....	107	76.6	83	40.9	15	40.0	38	34.2	123	57.7	9	55.5
1915.....	96	70.8	96	65.6	21	52.3	27	70.3	138	59.4	13	61.5

	Total Number of Deaths. 1911-1914.	Total Number of Autopsies. 1911-1914.	Percentage of Autopsies. 1911-1914.
1911.....	293	149	50.8
1912.....	305	160	52.4
1913.....	338	203	60.0
1914.....	375	211	56.2
1915.....	392	251	64.0

MONTHLY TABLE SHOWING PERCENTAGE OF AUTOPSIES—1915.

	Med. Service.		Surg. Service.		Gyn. Service.		Obst. Service.		Ped. Service.		Psy. Service.		Total.	
	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.	Number of Deaths.	Percent.of Autopsies.
Jan....	11	72.7	10	60.0	2	50.0	1	.....	9	77.7	1	.....	34	64.6
Feb....	5	20.0	8	50.0	..	.....	..	.....	5	60.0	1	100.0	19	47.3
Mar....	7	55.5	10	60.0	3	66.0	..	.....	8	62.5	1	100.0	29	65.4
April ..	13	76.9	4	75.0	1	.....	..	.....	13	84.6	1	100.0	32	78.1
May ...	8	75.0	7	55.5	3	100.0	..	.....	10	90.0	..	.....	28	78.1
June...	9	66.6	7	71.4	1	.....	2	.....	1	.....	1	.....	21	52.3
July...	4	100.0	8	50.0	3	100.0	2	50.0	23	47.9	1	.....	41	56.0
Aug....	5	100.0	6	83.3	2	.....	..	.....	19	57.8	2	50.0	34	61.7
Sept...	4	100.0	9	55.5	2	.....	..	.....	18	50.0	1	100.0	34	55.8
Oct....	9	44.4	4	100.0	2	100.0	4	100.0	16	56.2	2	50.0	37	64.8
Nov....	8	87.5	14	71.4	1	.....	10	80.0	8	25.0	2	100.0	43	67.4
Dec....	13	69.2	9	77.7	1	.....	8	75.0	8	62.5	1	100.0	40	70.0

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"THE MONDAY CONFERENCES."

During the past few years it has become increasingly difficult for the large number of physicians connected with the hospital to attend the post-mortem examinations, and almost impossible for them to acquaint themselves with the more detailed gross and microscopic studies made subsequently.

As a consequence the association between the clinical and pathological departments of the University—one of the ideals of the institution—was not so intimate as it had been. For this reason the Monday afternoon faculty conferences were inaugurated in the fall of 1914. Each Monday morning various members of the different departments receive a notice of the cases to be presented at the conference.

These cases are those which have come to autopsy and upon which the anatomical studies have been completed in the immediate past, usually the past week.

The clinical history is briefly presented by a member of the clinical staff. This is followed by a similar presentation and gross and microscopic demonstration of the anatomical findings. The case is then open to discussion to all present.

Usually from 4 to 5 cases are discussed at each conference. With few exceptions Dr. Welch has presided, and the success with which the conferences have been attended has been due in a large measure to his interesting discussions.

CLINICAL REPRESENTATIVES ON THE STAFF OF THE DEPARTMENT OF PATHOLOGY.

A further endeavor was made to bring the Department of Pathology into a more intimate relation with the clinical departments, by having a junior member of each clinical department serve for a year on the staff of the Department of Pathology.

The reason for this is that the more detailed autopsy studies are frequently greatly aided by an intimate knowledge of the clinical aspects of the case.

During the past year only two clinical departments, surgery and pediatrics, have been able to cooperate in this way.

DONATION.

The department has been very fortunate in the receipt of a sum of money which will greatly facilitate the more detailed bacteriological and immunological studies associated with the post-mortem and research work.

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THE RÔLE OF THE AUTOPSY IN THE MEDICINE OF TO-DAY.* †

By M. C. WINTERNITZ.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

The most convincing evidence of the importance of post-mortem examinations may be found in the history of medicine. As a result of the work of many centuries pathological anatomy, the basis of physical diagnosis and scientific therapy, became established through the systematic performance of autopsies.

The overthrow of the empirical medicine of the Ancients came with the dissection and the study of the more intimate anatomical structures of the human body nearly 2000 years after the establishment of scientific medicine by Hippocrates (460-377[?]B. C.).

In the writings of Vesalius (1414-1465), followed by those of Fallopius (1523-1562), Eustachius (1520-1574), and many others, many observations on morbid anatomical structure may be found. Benevieni (1440-1524), the pioneer in pathological anatomy, as well as his successor, Théophile Bonet (1620-1689), confined his attention mainly to a collection and description of monstrosities and curiosities.

Morgagni (1682-1771) was really the first to grasp the significance of pathological anatomy. He correlated the changes in the body found after death with the symptoms of disease, and incorporated his studies in a volume entitled, "De Sedibus et causis morborum per anatomen indagatis." His work was objective, based on personal observations at the post-mortem table, and marks one of the great epochs in medicine. Matthew Baillie (1761-1823) followed Morgagni closely with book and atlas.

* Read before the eighteenth annual conference of the American Hospital Associations, Philadelphia, Sept. 26-29, 1916.

† Published under the title "Autopsies—Their Value, Methods of Obtaining and Protection of the Hospital," Modern Hospital, 1917, January.

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Then came Bichat (1771-1802). He emphasized tissues, not organs, as the seat of disease—histology without the microscope. His views were based on sound observation and had an important bearing on that most brilliant period of French medicine, the first 30 years of the nineteenth century, illuminated by the work of Corvisart (1755-1821) and Laennec (1781-1826). Through him they saw in pathological anatomy the foundation of physical diagnosis. Their work bore fruit immediately in England, where Bright (1789-1858), Hodgkin (1798-1866), and Addison (1793-1860) correlated the clinical and anatomical pictures of their cases as indicated in part by the diseases which bear their names. Likewise in Vienna the co-operation between Rokitansky (1804-1878), whose knowledge of pathological anatomy has probably never been equaled, and the clinician, Skoda (1805-1881), created a school of medicine which became famous throughout the world as affording the best opportunity to study the relation of symptoms to the organic changes in the body. This was a period of exaggeration for pathological anatomy. So much emphasis was laid on the anatomical changes in the organs and tissues and these seemed so irreparable, that therapeutic nihilism was a natural consequence. This, in its turn, led to the rational therapy of to-day.

Rokitansky had laid the cornerstone of modern general pathology, and particularly of pathological histology. It remained for Virchow (1821-1902) to establish cellular pathology. This is his great monument. His influence on the progress of medicine cannot be overemphasized. He eliminated speculation, and recognized only actual deductions based on observation. He emphasized much more strongly than any of his predecessors the importance of objective knowledge in pathological conceptions. He taught that every physiological process possesses an anatomical corollary, and that disease consequently finds expression in anatomically visible change. Cohnheim (1839-1884), Virchow's pupil, concentrated on the field established by John Hunter (1728-1793), namely, experimental pathology, which won such an important position in the progress of medicine.

During the present generation, medicine has advanced very rapidly. Through bacteriology the direct cause and prevention of many diseases have been determined. The application of new methods, largely derived from progress in other purer sciences, physics and chemistry especially, have also played an important rôle. These have led so rapidly to the creation of new phases of medicine that for the moment, perhaps,

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it is necessary to stop and consider the rôle of the autopsy in the medicine of to-day.

The autopsy furnishes the only means of teaching the student pathological anatomy; it controls clinical diagnosis and therapy; it is the only reliable evidence on which vital statistics may be based; it is a constant source of problems necessary for the advancement of medicine. Naturally, therefore, the greatest benefit is derived from the autopsy in an institution where teaching is combined with clinical and research facilities. The realization of this has made pathology the most important link between the hospital and the medical school. The more intimate this affiliation, the closer the proximity of the two institutions, the greater are the mutual advantages.

The autopsies from the hospital are essential for the teaching of the medical student. Only under exceptional circumstances is it possible for the hospital to have the laboratory facilities and the large and efficient staff which affiliation with a teaching institution offers. The pathologists of such an institution not only constantly augment their knowledge by the correlation of the clinical and anatomical findings with physicians of the hospital, but the oft-repeated review necessitated in the teaching of the elementary aspects of the subject frequently opens new avenues of approach to unsolved problems.

A department of pathology as outlined above not only furnishes teaching facilities, but is a means of deriving great benefit from the autopsy and its subsequent study. Briefly, it must have facilities for the post-mortem examination, equipment for the histological examination of the tissues, including the most specialized types of apparatus required for neurological and other more or less specific branches of clinical pathology; laboratories of experimental pathology, including bacteriology, physiology, chemistry, and, finally, a recording department where the completed files of the autopsies may be analyzed to the best advantage. This is only the shell; a more important need is men specially trained in these various branches to direct the work. The subject has outgrown the scope of the individual.

The student comes to such a pathological laboratory after he has dissected one-half of the human body. He has a practical knowledge of the skeletal system and, most valuable of all, if he has acquired it, independence of thought and work. His knowledge of gross anatomy is based on the limited dissection of the skeleton and the much more limited opportunity to study the viscera, and then only in embalmed

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bodies. His knowledge of histology is based on a few typical tissues, usually animal tissues and, as a rule, he has little conception of gross and microscopic anatomical correlation.

The autopsy may be made to appeal strongly to the student. It deals with diseases in man, the subject he has elected as his life work, and brings him into much more intimate contact with clinical medicine. After he has seen a large number of autopsies, he is able to recognize the physiological range of variation in organs and tissues and then the more gross and characteristic anatomical manifestations of disease. This knowledge is not easily acquired, for he must first learn to look at things as they are, to see what they really show, and not as he has read they should be. In short, he must acquire the power to see things objectively. He can often make a diagnosis from a description similar to one which he remembers from a book, although the object or condition itself, when shown to him, will remain unrecognized. Familiarity with gross pathology can be acquired only at the autopsy table. Here, too, the student has the opportunity of correlating the gross and microscopic anatomical pictures. He sees and makes sections of the gross tissues which he has studied. His opportunities do not stop here. He sees the lesions produced by bacteria in man which he has heretofore been able to study only in the test-tube or, at most, by animal inoculation. He has the opportunity of studying these bacteria in smears, by cultivation and by inoculation into animals. He studies the resultant lesions and finally recultivates the bacteria in many cases. In this way only can he be made to realize the importance of Koch's postulates in the etiology of disease. In this way, too, he learns the difference between the organism he has studied in his course in bacteriology, often attenuated by long artificial cultivation, and the virulent organism freshly removed from its parasitic existence. Likewise, he has the opportunity of doing immunological tests upon the tissues of the host and the parasite. But the student's opportunities do not end even then. He hears the results of chemical, physiological and other studies carried out in the various laboratories of experimental pathology, and not infrequently the opportunity to share a small part of a problem in such a laboratory stimulates him to psychic independence.

The advanced student and the clinician return to the post-mortem room with questions. They know the clinical history and they are interested in the many problems the case presents. They acquire in this way an anatomical picture which they correlate with their clinical

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findings. The more autopsies the clinician has seen, the keener is his interest. He views future cases from the composite mental picture he has formed at the autopsy table, and modifies his diagnosis, prognosis and treatment accordingly with scientific accuracy.

The complete study of an autopsy has become so complicated that the routine procedure alone requires days and even weeks. The advanced student and the clinician should know the result of these investigations, and for this purpose the modern clinical pathological conference serves admirably.

There are two types of conference. The older, used essentially to compare briefly the anatomical and clinical aspects of cases for medical students, a teaching conference, where, as a rule, it is impossible to enter into detail on the more obscure aspects of the case. The modern autopsy demands a more advanced type of conference, where, after a brief presentation of the clinical aspects, together with charts, X-ray plates, etc., the anatomical demonstration of the organs is supplemented by gross and microscopic pictures of the important lesions of the case and by reports from the bacteriologist, chemist and others engaged in the unraveling of the various problems that have presented themselves. This is all done very briefly, and is followed by a discussion in which many of the faculty, which should be well represented, join. Such conferences give a new impulse to research, and many interesting problems have evolved through them from the autopsy.

The proper recording and filing of the autopsy protocols make them one of the hospital's most valuable assets. The protocol should be an objective description of the autopsy, made during its procedure. It should be supplemented by a synopsis of the clinical history and by the objective description of microscopic sections, primarily of tissues, the seat of gross lesions, but also from all other important organs of the body. The results of special investigation in the various units of the laboratory of experimental pathology should likewise be recorded with the case. Photographic illustrations of gross and microscopic lesions add greatly to the clearness of the description. The anatomical diagnosis should not be written until a complete study of the case has been made. A provisional anatomical diagnosis may be made at the time of autopsy for the convenience of the members of the staff of pathology as well as for the clinician, but it is evident that, since the ideal anatomical diagnosis is the sequential statement, not only of the anatomical changes, but also of the results of laboratory study in relation to the

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immediate and ultimate cause of death (as well as a tabulation of subsidiary findings), it cannot be completed until all the evidence is at hand.

Records completed in this way can be made of the greatest value. They not only furnish an ever-increasing basis for research in specific diseases, but on their analysis the inaccurate vital statistics of to-day will ultimately be corrected.

In the evolution of man, new medical problems will constantly present themselves, and in their study the rôle played by the autopsy in the successful solution of similar problems of the past will repeat itself. The most accurate knowledge we have of the scourge of the present day, infantile paralysis, is its pathological anatomy. Without the autopsy the diagnosis even of this disease often cannot be attained. From the anatomical picture the clinical manifestations of the disease are readily understood and its successful transmission to animals has been verified. Its histology, comparable to that of other infectious diseases, will aid in establishing its etiology and ultimately may help in unraveling its portal of entry and dissemination in the body.

This brief review has been made in an attempt to emphasize the importance of the autopsy for the progress of medicine. The knowledge gained through the post-mortem examinations of the past is permanent. The problems still to be solved are very numerous, and in these not only must the autopsy play its rôle, but it must be performed in ever-increasing numbers for its value in fundamental medical education. The student must learn pathological anatomy. The physicians who have been taught to think anatomically must be given opportunity to enlarge their experience. The community must have accurate vital statistics. It is not sufficient that post-mortems are carried on in large numbers in Europe—they must be performed in every country, in every community, if the health of the public is to be safeguarded.

There is, unfortunately, a great discrepancy between the number and percentage of autopsies in the larger European hospitals and those of the United States. This has been emphasized recently in the report of the Committee of the New York Academy of Medicine.* To facilitate comparison, the figures in their tables have been calculated for a period of three years and are presented in Table I.

* **Report on Post-mortem Examinations in the United States by the Public Health, Hospital, and Budget Committee of the New York Academy of Medicine. Jour. Am. Med. Assn., 1913, LX, No. 23, p. 1784.**

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TABLE I.

Number of autopsies.		Canada.		England.		Germany.		Austria. *		United States.	
(A) Total.	(B) Percentage.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.
1–25	1–10	....	....	....	....	....	....	....	....	.....	5
25–50	10–20	....	....	....	....	....	....	....	....	.....	5
50–100	20–30	....	1	....	....	....	....	....	....	2	4
100–250	30–40	1	....	....	....	....	....	....	....	5	1
250–500	40–50	....	....	....	....	....	....	....	....	5	1
500–1,000	50–60	2	....	1	1	2	....	....	....	5	.....
1,000–1,500	60–70	....	1	2	....	....	....	....	....	.....	1
1,500–2,000	70–80	....	....	2	2	....	....	....	....	.....	.....
2,000–3,000	80–90	1	....	....	2	....	3	....	....	.....	.....
3,000	90–100	....	....	1	....	4	3	1	1	.....	.....

* The combined statistics of eight Austrian hospitals have been omitted. The numerals in the various columns A and B represent the number of institutions in the countries indicated that have a total number of autopsies (A) and a percentage ratio of autopsies to deaths (B) to correspond with the respective figures on the left of the chart.

This table shows not only how few autopsies are performed in a number of representative hospitals of the United States compared with those of the other countries, but it suggests that there may be an almost proportionate variation between number and percentage. Further analysis of the individual hospitals in this country shows that this relationship does not hold.

TABLE II.

Hospital.	Autopsies.	
	Total number.	Percentage.
1	61	39.6
2	76	10.
3	104	16.8
4	117	13.1
5	120	17.2
6	158	7.3
7	167	26.9
8	281	24.5
9	284	29.6
10	313	23.
11	346	62.6
12	408	9.2
13	670	45.1
14	779	7.5
15	813	13 7
16	927	14.3
17	998	10.

Recently published data from several hospitals in the United States show a marked improvement in the ratio of autopsies to deaths. The

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director of the Pathologic Institute of the Cincinnati General Hospital, Dr. Paul G. Woolley, reports that between June 1 and December 31, 1915, 293 necropsies were held from a total of 465 cases, a percentage of 63.* Since the Robert Breck Brigham Hospital, Boston, opened on April 1, 1914, complete autopsies have been carried out on 70 per cent of all those dying (35 autopsies in 50 deaths),† and at the Mayo clinic during the triennial period, 1910-12, for 626 deaths, 512 necropsies were made, or 81.8 per cent; in 1913 there were 269 deaths and 227 necropsies, or 84.4 per cent; in 1914, 293 deaths and 258 necropsies, or 88 per cent, while to date (March 17, 1915) there have been 73 deaths with 73 necropsies, or 100 per cent.‡

These percentages, unequaled by any other institution in the United States, and by few abroad, as well as by our own experience at The Johns Hopkins Hospital and the City Hospitals at Bay View, Baltimore, have led to the belief that an inquiry into the method of obtaining autopsies, the use made of the autopsy material, etc., from a group of large institutions, might be of interest. A circular letter was therefore sent to the superintendents or the pathologists of a number of hospitals in the United States. Twenty responses were received.§ The results of this investigation are, in part, tabulated in Tables III and IV.

In 19 of the 21 hospitals included in the investigation, there has been no notable change in either the total number or percentage of autopsies during the past six years.

If, however, the ratio of autopsies to the number of deaths for any year—say, 1915—be compared with similar data (Column B, Table I) from the report of the Committee of the New York Academy of Medicine, the result is very surprising, especially if the 21 hospitals included in this investigation are supplemented by the Robert Breck Brigham Hospital, Boston, The Johns Hopkins Hospital, and City Hospitals, Bay View, Baltimore, for the same year.

The above comparison is encouraging, the more so, perhaps, since 11 of the hospitals included in Column B of Table IV (present investigation) are also included in Column A (Report of the Committee of

* More Good Autopsy Figures; The Modern Hospital, 1916, VI, p. 376.

† Recent Necropsy Records in the United States; Jour. Am. Med. Assn., 1916, LXVI, pp. 1706-1707.

‡ Wilson, L. B., The Necropsy as a Public Service; Jour. Am. Med. Assn., 1915, LXIV, No. 19, p. 1560.

§ I wish to take this opportunity of thanking the superintendents and pathologists of these institutions for their kind co-operation.

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TABLE III.

Hospital.	Number of deaths.	Percentage of autopsies.	Requests for autopsy.		Signature required.
			Per cent.	By whom.	
Mayo Clinic...	1910, 198	81.	100	Pathologist...	Person who obtains permission.
	1911, 200	86.			
	1912, 227	86.			
	1913, 269	84.			
	1914, 293	88.			
	1915, 338	95.			
Pennsylvania..	1910, 349	33.8	90+	Physician....	Verbal consent.
	1911, 328	27.3			
	1912, 303	27.5			
	1913, 339	36.4			
	1914, 379	35.5			
	1915, 286	40.			
Presbyterian...	1910, 433	28.9	100	Physician....	Relatives, hospital superintendent, obtainer.
	1911, 398	20.4			
	1912, 323	25.1			
	1913, 286	29.3			
	1914, 306	35.6			
	1915, 278	40.			
Worcester City.	1910, 407	9.8	50	Physician....	Relatives.
	1911, 381	4.9			
	1912, 423	9.2			
	1913, 473	7.8			
	1914, 473	7.4			
	1915, 538	4.4			
Montefiore.....	1910, 105		50	Hospital superintendent.	Witnessed by two relatives.
	1911, 124				
	1912, 106	26.07			
	1913, 104				
	1914, 197				
	1915, 228				
Cincinnati General.	1910, 223	?	100	Physician, hospital superintendent, undertaker.	Relatives, hospital superintendent.
	1911, 93	?			
	1912, 95	?			
	1913, 70	?			
	1914, 71	?			
	1915, 369	?			
Michael Reese..	1910, ?	?	?	Physician....	Relatives, hospital superintendent, obtainer.
	1911, ?	?			
	1912, ?	?			
	1913, ?	?			
	1914, ?	?			
	1915, ?	?			

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TABLE III.—CONTINUED.

Hospital.	Number of deaths.	Percentage of autopsies.	Requests for autopsy.		Signature required.
			Per cent.	By whom.	
Lakeside.....	1910, ?	?	100—	Physician....	Relatives, hospital superintendent, obtainer.
	1911, 232	40.			
	1912, 213	40.			
	1913, 148	43.			
	1914, 222	38.			
	1915, 243	44.			
Grace.....	1910, ?	?	25	Physician....	Relatives, obtainer.
	1911, ?	?			
	1912, ?	?			
	1913, ?	?			
	1914, ?	?			
	1915, 317	9.1			
Boston City....	1910, 1,663	10.2	65	Physician....	Relatives, obtainer.
	1911, 1,833	6.1			
	1912, 1,834	5.5			
	1913, 1,891	5.3			
	1914, 1,827	6.8			
	1915, 1,932	9.8			
University Philadelphia.	1910, 303	14.	50	Physician....	Relatives, obtainer.
	1911, 271	12.			
	1912, 249	18.			
	1913, 308	14.			
	1914, 290	17.			
	1915, 310	20.			
BuffaloGeneral.	1910, 280	13.	50	Physician....	Relatives, hospital superintendent.
	1911, 340	11.+			
	1912, 344	12.+			
	1913, 355	12.			
	1914, 360	13.			
	1915, 368	11.			
New York.....	1910, 690	22.89	100	Physician....	Relatives, hospital superintendent, obtainer.
	1911, 708	23.44			
	1912, 663	28.05			
	1913, 606	26.07			
	1914, 592	22.12			
	1915, 562	27.4			
New Haven....	1910, 254	15.	?	Physician....	Relatives.
	1911, 235	8.			
	1912, 268	9.			
	1913, 307	9.+			
	1914, 332	9.			
	1915, 299	10.			

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TABLE III.—CONTINUED.

Hospital.	Number of deaths.	Percentage of autopsies.	Requests for autopsy.		Signature required.
			Per cent.	By whom.	
Cleveland City.	1910, ?	?	50	Physician....	Relatives, hospital superintendent, obtainer.
	1911, ?	?			
	1912, 644	18.3			
	1913, 842	16.7			
	1914, 755	21.9			
	1915, 845	23.4			
Mt. Sinai.....	1910, 646	23.	?	Physician, hospital superintendent.	Relatives, hospital superintendent, obtainer.
	1911, 719	21.			
	1912, 738	20.			
	1913, 705	10.			
	1914, 607	12.			
	1915, 750	14.			
University of California.	1910, 66	20.	50	Physician....	Relatives, hospital superintendent.
	1911, 51	41.			
	1912, 43	58.			
	1913, 80	52.5			
	1914, 101	59.4			
	1915, 112	73.2			
Massachusetts General.	1910, 450	56.+	100	Physician....	Relatives, hospital superintendent, obtainer.
	1911, 475	45.—			
	1912, 470	34.+			
	1913, 428	34.+			
	1914, 426	27.+			
	1915, 405	28.—			
Barnes.....	1910, ?	?	100	Physician....	Relatives, hospital superintendent.
	1911, ?	?			
	1912, ?	?			
	1913, ?	?			
	1914, 2	50.			
	1915, 98	50.6			
St. Louis Children's.	1910, ?	?	100	Physician....	Relatives, hospital superintendent.
	1911, ?	?			
	1912, ?	?			
	1913, ?	?			
	1914, 8	50.			
	1915, 145	75.			
Bellevue.....	1910, ?	10.	?	Physician....	Relatives, hospital superintendent, obtainer.
	1911, ?				
	1912, ?				
	1913, ?				
	1914, ?				
	1915, ?				

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the New York Academy of Medicine). While there are still a large number of hospitals with a small percentage of autopsies, and many of these have a large number of deaths, nevertheless it is evident that there is an increasing group of institutions where the percentage of autopsies is high. Perhaps the selection of hospitals was fortuitous, and it is probable that further investigation of many more institutions would yield a still different result.

TABLE IV.

Column B. Invest'n of Com. N. Y. A. M.	Percentage of autopsies.	Column A. Present invest'n.
5.....	1–10	5
5.....	10–20	3
4.....	20–30	4
1.....	30–40	2
1.....	40–50	2+1=2*
.....	50–60	1
1.....	60–70	0+2=2+†‡
.....	70–80	2
.....	80–90	1
.....	90–100	0

* City Hospitals, Bay View, Baltimore, 45.4 per cent for 1915.
† Johns Hopkins Hospital, 1915, 65 per cent.
‡ Robert Breck Brigham Hospital for 1914, calculated as 68 per cent.

Requests for Autopsies.

It is very surprising, indeed, that in such splendid hospitals as are represented in the present investigation an attempt is not made to obtain an autopsy for every death. This, unfortunately, is not the case for the majority. Only nine of the 20 hospitals request permission in 100 per cent of the fatal cases, one in 90 per cent, and seven in from 25 to 65 per cent. The remaining four gave no definite information on this point.

It may be said with certainty that as yet the people of the United States have not reached that stage of evolution when they will request the institution to perform autopsies. Permission for the performance of the autopsy is requested by a number of different people. For convenience, these may be grouped under physician and hospital superintendent. Physician includes intern (resident and attending), hospital superintendent, assistant, and lay clerks. The physician requests permission for the autopsy in twelve, the hospital superintendent in two, both physician and hospital superintendent in six, and in only one case

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is the responsibility delegated to the pathologist. The physician succeeds in from 5 to 44 per cent, the hospital superintendent in 28 to 75 per cent, the physician and hospital superintendent in 4.4 to 23 per cent, and the pathologist in 95 per cent. It is dangerous to draw deduction from such an analysis as the above. It is not "who," but "how."

Dr. Summersgill, superintendent of the University of California Hospital, where they have been so successful in increasing the percentage of autopsies recently, was kind enough to comment on the question:

I have observed many times that a clever lay clerk will secure more post-mortems than an ordinary medical man, as it is a natural tendency for so many unintelligent people to believe that a physician is hard-hearted and desires a post-mortem mainly to satisfy his curiosity, and for that reason I believe that a good lay clerk can secure better results with this class of people than a medical man.

In a recent publication,* Wilson emphasizes that one person only, the pathologist or his assistant, should be allowed to present the subject of necropsy to the relatives of the deceased. Although the senior fellow in pathology, who is delegated to this duty by Dr. Wilson, serves only six months, the fact that their necropsy service has not fallen below 80 per cent in the last six years is sufficient evidence that success in obtaining permission for a post-mortem examination is not entirely a matter of personality, but more largely one of "training in placing proper argument before the relatives."

Answer to the question, "What do you consider the most successful argument in obtaining autopsies?" could hardly be made in detail in the brief space allotted to it in the circular letter. The information received, however, shows a certain uniformity of method. The stock arguments are (1) the importance of the autopsy in determining the true cause of death, (2) the benefit derived from this knowledge by the family, (3) by the hospital, (4) by the science of medicine and humanity, (5) the aid of the exact cause of death as revealed by the autopsy in the settlement of insurance claims.

The answers to several other questions may be summarized here, for they have a definite bearing on the two arguments which are most widely used in obtaining permission for autopsy.

* **Wilson, L. B., The Necropsy as a Public Service; Jour. Am. Med. Assn., 1915, LXIV, No. 19, p. 1560.**

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In no instance does the hospital make any effort to inform the family of the result of the post-mortem examination. Many of them are willing to do so when requested, and many of them feel that it should be done only when necessary. The benefit, therefore, to the family can be only a remote one, and conditions frequently revealed by the autopsy, important for the immediate or future welfare of the family, remain unknown to them.

One of the ways in which autopsies may "help others" is through correct vital statistics. The answers to the query, "Are health certificates completed in conformity with the anatomical findings?" are difficult to understand. Three institutions gave an indefinite answer, such as "more or less," "when possible," and "fifty-fifty"; one in "cancer cases, otherwise not"; four answered "No," and the other remaining 12 said "Yes." One of the latter, Bellevue Hospital, New York, has a special form for this purpose, which Dr. Norris was kind enough to inclose in his reply, with the following note:

Owing to the difficulty and delay caused in sending the death certificate book to the pathological laboratory to fill in the autopsy findings, and because death certificates are given to the undertakers in order that they may obtain removal permits more promptly, the Department of Health has issued a blank entitled, "Return of Autopsy Findings," which I inclose. The anatomical diagnosis is filled out on this sheet.

RETURN OF AUTOPSY FINDINGS.

Date.....191..

TO THE DEPARTMENT OF HEALTH:

The results of the autopsy performed on the body of

.....

who died at.....
(Name of institution)

on.....are as follows:
(Date)

.....

.....

.....

.....

.....

Signature.....
Pathologist.

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The New York State Board of Health may be congratulated on this method, which is the only way in which vital statistics can be accurately compiled. It would be gratifying indeed if similar methods had already been adopted in all of the hospitals that answered the query in the affirmative. Unfortunately the information obtained in this investigation is not far-reaching enough to say this with certainty, and it is feared that it is not the case.

In Maryland, for instance, the death certificates must be completed before the burial permit is granted, and as a consequence it is usually filled out with the clinical diagnosis. In obscure cases, where the clinical diagnosis is not definite, the completion of the death certificate is delayed until the gross anatomical findings are known. Even with this knowledge, however, the anatomical diagnosis is incomplete in a large number of cases until histological, bacteriological, and other special investigations have been made. Consequently this information, invaluable in the compilation of vital statistics, is, at best, buried in the records of the hospital. Without more definite knowledge, it may be assumed that the condition in the state of Maryland is not unique.

With the aid of the Prudential Life Insurance Company an investigation of the autopsy records, which includes a comparison of the clinical and anatomical diagnosis with the records of the State Board of Health—namely, the certified and classified cause of death—has been undertaken in Baltimore at The Johns Hopkins and at the City Hospitals. The information derived from this study will undoubtedly assist in determining the accuracy of vital statistics.

It is evident from the following note kindly included in the answer of Dr. A. R. Warner, of Cleveland, that the undertaker may be of aid in obtaining autopsies. He says:

Recently I was at the Cincinnati Hospital, and I find that there is in use there a co-operation between the hospital and a school of embalming, whereby the school of embalming embalms, free of charge, all bodies autopsied. It is understood between this school and the city undertakers that this will be done in all autopsied cases, and the undertakers do not therefore object to autopsies. The embalming is done for them and well done, and they collect the usual fee. It is, therefore, for their interest to have autopsies, and the usual antagonism is entirely missing. This has been a great help to them in securing autopsies.

At The Johns Hopkins Hospital all autopsied bodies have been embalmed for the past three years, and it has had a similarly good effect in conciliating the undertaker to the delay the post-mortem

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frequently imposes. Occasionally, however, in the request for permission to perform the autopsy, the fact that the body is embalmed by the hospital free of charge has been utilized with success as an argument. The possible conflict here should be avoided.

From the answers received it is apparently not of moment, as far as the success in obtaining post-mortem examinations is concerned, whether the institution requires the signature of the nearest relative, the hospital superintendent, or the individual who obtains permission. The Mayo clinic, for instance, with the highest percentage of autopsies, requires only the signature of the person who obtains permission, whereas at the University of California, where the percentage of autopsies has increased from 20 to 73 in the past six years, the signature of the nearest relative and that of the hospital superintendent are both required. Undoubtedly the latter method will insure a maximal protection to the institution. On the other hand, despite the result of the present investigation, it is generally assumed that the necessity of obtaining the signature of a relative, particularly from the more ignorant, may result in failure, when a verbal consent for a necropsy would be granted. Such a signature, if not absolutely necessary for the protection of the hospital, should be dispensed with.

The experience of the past few years at the department of pathology of the City Hospitals, Bay View, Baltimore, may be of interest. At Bay View the municipal almshouse and the hospital are closely affiliated and are under the direction of the same superintendent. In 1912 the work in pathology was reorganized. With a small expenditure of money the facilities for post-mortem examinations were made attractive, and a laboratory for histological, bacteriological, and chemical studies was equipped. A resident was appointed, and under his direction the interns of the various clinical branches performed the autopsies during a part of their service. The autopsies were carefully studied and recorded. A weekly clinical pathological conference was inaugurated, and the material from the autopsy further utilized for the teaching of gross morbid anatomy to the students of two of the medical schools of the city.

Before 1912 the post-mortems were performed at the City Hospitals by the resident pathologist of The Johns Hopkins Hospital or one of his assistants. He had to carry with him the autopsy kit, and he brought back such material as he was personally interested in, or that he felt was essential for his course in gross morbid anatomy. He rarely

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JOHNS HOPKINS HOSPITAL.

Table Showing Percentage of Autopsies.

Year.	Medical service.		Surgical service.		Gynecological service.		Obstetrical service.		Pediatric service.		Psychopathic service.	
	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.
1911	122	74.5	136	33.0	25	36.0	10	40.0	.....	.....	.....	.....
1912	151	70.8	116	31.8	27	25.8	11	81.8	.....	.....	.....	.....
1913	108	85.1	107	34.5	22	36.3	4	17.5	92	57.6	5	100.
1914	107	76.6	83	40.9	15	40.0	38	24.2	123	57.7	9	55.5
1915	96	70.8	96	65.6	21	52.3	27	70.3	138	59.4	13	61.5

	Total number of deaths 1911—1914.	Total number of autopsies 1911—1914.	Percentage of autopsies. 1911—1914.
1911	293	149	50.8
1912	305	160	52.4
1913	338	203	60.
1914	375	211	56.2
1915	392	251	64.

Monthly Table Showing Percentage of Autopsies, January to September 19, 1916.

Month.	Medical service.		Surgical service.		Gynecological service.		Obstetrical service.		Pediatric service.		Psychopathic service.	
	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.	Number of deaths.	Per cent of autopsies.
January...	7	100.	9	55.5	1	100.	10	80.	7	42.8	1	.....
February..	7	71.4	5	60.	1	100.	9	88.6	12	66.6	2	100.
March	5	60.	11	81.8	2	100.	6	100.	13	69.2	1	100.
April	17	82.6	9	44.4	2	100.	6	100.	15	73.5	.....	.....
May	12	83.4	6	50.	2	100.	10	80.	13	53.5	.....	.....
June.....	16	62.5	8	25.	3	100.	11	81.8	9	77.7	.....	.....
July	7	85.7	10	70.	1	100.	6	100.	23	43.4	1	.....
August....	8	75.	3	66.2	3	66.2	11	81.9	17	65.	.....	.....
September.	3	100.	2	50.	.....	.....	4	75.	5	80.	1	.....

Summary—Number of deaths, 868. Number of autopsies, 261. Percentage of autopsies, 70.9.

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knew anything of the clinical aspects of the case, and the only record of the autopsy was a hasty anatomical diagnosis based on the gross findings alone. The result of the reorganization was very gratifying. The autopsies increased in total number from 75 to 297, and in percentage from 12.3 to 60. A friendly rivalry sprang up among the interns and the residents of the various clinical branches to obtain autopsies. Recent graduates were attracted by the possibility of supplementing their clinical work with the experience in pathology, and made the problem of securing competent interns less difficult. Several of these interns have subsequently increased the interest in pathology and greatly assisted in augmenting the number of autopsies in other institutions where they have since been located.

At The Johns Hopkins Hospital the number and percentage of autopsies have also increased during the past few years, as is evident from the table on the preceding page.

Conclusion.

In order to obtain large numbers of autopsies, it is necessary to request them in every fatal case. It does not suffice that the individual who seeks permission for the post-mortem examination is interested in the outcome of his argument—everyone in the institution must be anxious for him to be successful. The only way this can be accomplished is to give to each one a return for this interest and co-operation. The physician and the hospital superintendent must realize the benefit that accrues to him individually from the systematic performance of post-mortem examinations. As important as these individuals may be, the family and community are even more so. They should not only benefit through the educational value of the autopsy to student and physician, but the family should be told honestly, fully, and in simple language just what the findings are, the bearing these may have on the health of its other members, and, as far as this is possible, they should be told how they can protect themselves. The community should be given accurate vital statistics.

When all concerned realize that they are constantly receiving a return for their interest and co-operation in increasing the number of autopsies, it will no longer be necessary to discuss methods of obtaining them and protection for the hospital—autopsies will be demanded.

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EXPERIMENTAL NEPHROPATHY IN THE DOG.

LESIONS PRODUCED BY INJECTION OF *B. BRONCHISEPTICUS* INTO THE RENAL ARTERY.

By M. C. WINTERNITZ, M. D., and WILLIAM C. QUINBY, M. D.

(From the Department of Pathology of The Johns Hopkins University and from the Brady Urological Institute of The Johns Hopkins Hospital.)

Spontaneous renal lesions are not uncommon in the dog. As a rule they are inconspicuous, but occasionally extensive anatomical changes occur similar, even in their detail, to those found in the human kidney in the progressive, non-suppurative types of nephritis.

The etiology of the disease in the dog is probably more obscure than in man, for it has received very little attention. It is immediately evident, however, that the two conditions may result from similar causes. The great majority of chemical irritants already used for the production of experimental renal lesions can have no more place in the etiology of these spontaneous changes in the dogs than they have in the pathology of the human kidney. Promising experimental results have been obtained recently with bacteria as the exciting agent—a fact that is in accord with the growing impression that microorganisms may be etiologically associated with the more important types of progressive nephropathies in man.

Assuming this impression to be correct, it is probable that the nephropathy of the dog is the result of some acute infectious disease frequent in the species. Accordingly, in the experiments here recorded, the attempt to produce a progressive nephropathy in the dog similar to those in man differs in method from the usual procedures, in that a microorganism, *B. bronchisepticus,* known to produce spontaneous disease in the species, has been employed.

For purposes of comparison the following spontaneous case is described:

SPONTANEOUS CASE.—The animal, a full-grown mongrel, was in good general health. Under the influence of paraldehyde (1.7 gm. per kilo of body-weight) the region of the prostate had been exposed to 112 mg. of radium bromide for about five hours. The animal recovered from the anesthetic, but the next morning was found dead in the cage.

Autopsy.—There are no lesions other than those of the kidneys. These organs are much contracted and removal of the adherent, thickened capsules shows a coarsely granular surface. On section, the cortex of the

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kidney is irregularly and markedly thinned; the striations are obscured. The pyramids are somewhat decreased in size and the entire kidney has a pale brownish color.

Microscopic examination shows a good deal of patchy scarring throughout the cortex and upper portion of the pyramids. The scars are dense, infiltrated to a slight extent with mononuclear cells, and the renal parenchyma in these scars shows the usual retrogressive changes. The tubules are greatly dilated, except in the scarred areas, where they are very small and show a low epithelium; they may contain casts or cellular detritus. The dilated tubules are lined with a high columnar epithelium, which shows considerable vacuolation. Their lumina contain granular detritus and an occasional cast. The glomeruli are enlarged; in some places they appear more numerous, in others less frequent than normal. None of them appears entirely normal. The glomerular capsules are delicate, except in the scarred areas. The glomerular spaces are large. They contain serum and occasionally mononuclear cells. The tufts are swollen, very cellular and show various changes including hyaline thrombi, partial or complete hyalinization, intercapillary adhesions and adhesions between the tuft and capsule. The blood-vessels, except in the scarred areas, do not seem to be markedly affected. The tubules, in the upper portion of the pyramids especially, are dilated and irregularly tortuous; their epithelium is, for the most part, cubical and in some places seems to be stratified. Occasional tubules are found, so irregular in shape that they must have been formed by a rupture of the separating wall between several adjoining tubules. (See Figs. 1 and 2.)

Method.—The organism used for injection corresponded in its microscopical characteristics, staining qualities, cultural reactions and pathogenicity for lower animals to the *B. bronchisepticus*.

About 5 c. c. of either a 36- to a 48-hour growth in litmus-milk or of an emulsion of a growth from an agar slant in sterile salt solution were injected directly into the renal artery. At first both, later only one kidney was injected. The remaining one was subsequently injected in a similar manner or removed after the acute symptoms following the initial procedure had subsided.

All operations were done under ether anesthesia and with complete surgical asepsis.

The kidney was reached by a longitudinal abdominal incision usually about 10 cm. long and 1 cm. from the middle line, through which the intestines were withdrawn from the abdomen and covered with towels. By lifting the kidney from its bed, and using gentle, blunt dissection, it was possible to isolate the renal artery without trauma to its accompanying nerves. The culture was introduced directly into the artery through a fine, bent hypodermic needle, after temporary interruption of the blood stream by a *serre-fine*. After injection, the vein was compressed for a few seconds, subsequent to the release of the arterial circulation, in order to secure complete spread of the bacterial emulsion throughout the kidney. The kidney was then put back into its normal position, the intestines were replaced, and the abdomen was carefully closed in layers with silk.

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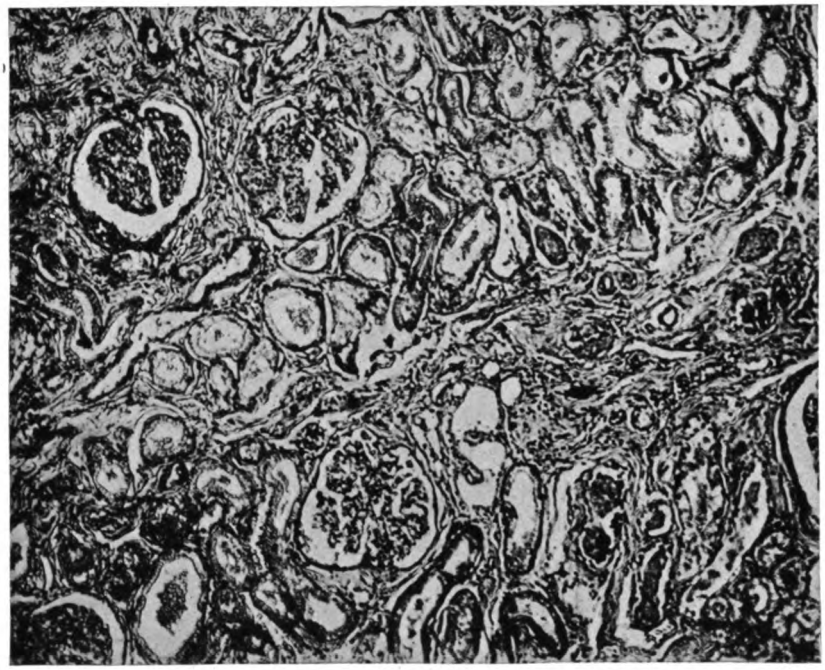

FIG. 1.

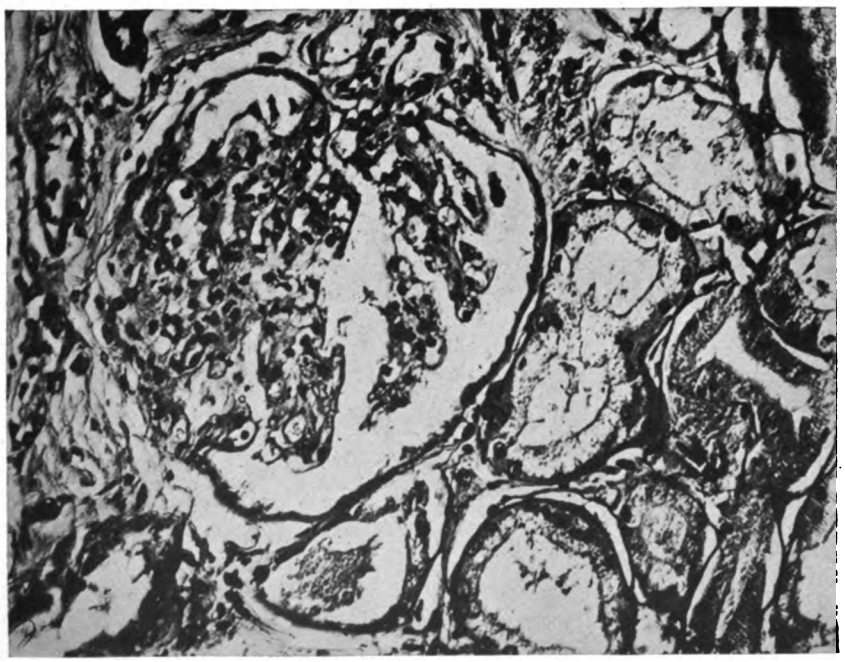

FIG. 2.

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As will be seen from the protocols, the immediate results of this procedure varied markedly. Some of the animals showed definite generalized distemper, with conjunctivitis, nasal discharge, anorexia and loss of weight. Their urine at first contained some blood and showed large amounts of albumin. On the other hand, other dogs showed no signs whatever of a general infection and, after the first few days, only the slightest traces of albuminuria. The larger number of animals reacted to the injection definitely, but without the severe generalized infection of the first group. It seems reasonable to explain these results on the ground of variation in susceptibility of the different animals. The severe, overwhelming infections occurred as a rule in young dogs, whereas the animals that showed practically no reaction were old, or had at least attained their full growth. This observation coincides with the well-known immunity which commonly follows an attack of distemper.

It is possible, therefore, to divide the animals into three groups.

1. Immune animals that showed only a transient renal lesion and no general reaction.

2. Animals that died acutely with a fulminating renal lesion and an acute general reaction.

3. Those that showed a milder renal lesion which progressed after the less severe general reaction had subsided. In this last group the animals ultimately succumbed to renal insufficiency, provided the uninjected kidney was removed shortly after the acute stage had passed.

An illustrative protocol for each of the above groups has been selected from a large number and is presented below:

GROUP I.

Immune Animals That Showed Only a Transient Renal Lesion and no General Reaction.

Illustrative Case.—Dog 27, a full-grown male. On March 18, 1916, under ether anesthesia a laparotomy was performed and 5 c. c. of a milk culture of *B. bronchisepticus* were injected into the right renal artery. The animal recovered from the operation promptly. On March 21 the urine contained a moderate number of casts, small round cells, and 1 gm. of albumin to the liter (Esbach).

The urinary changes persisted; on March 24, 200 c. c. of slightly cloudy urine, obtained by catheter showed a sp. gr. of 1,031, albumin 0.5 gm. per liter, and many casts and cells in the sediment. Under ether anesthesia, the abdomen was again opened and the lower third of the uninjected left kidney resected. The right kidney was found much enlarged, with injected

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capsular vessels and mottled surface. A wedge-shaped piece was resected for histological examination.

Section of Kidney Six Days After Injection.—The capsule of the kidney is uniformly thickened by a very vascular granulation tissue which is replacing an exudate of serum, red blood cells, and relatively few polymorphonuclear leucocytes. This inflammatory process extends into the renal

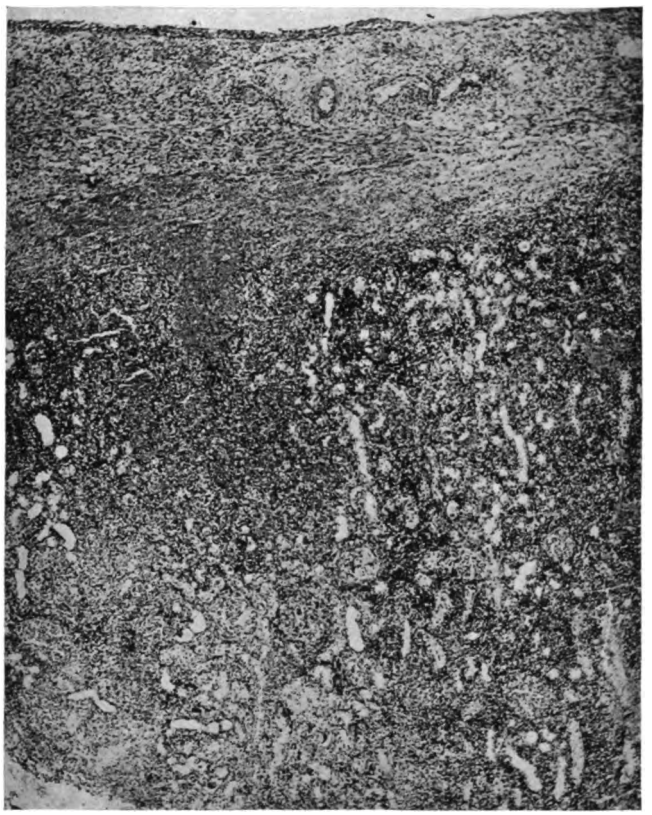

FIG. 3.

parenchyma only in focal areas, and here the interstitial tissue shows great engorgement of the capillaries, infiltration with mononuclear cells and occasionally polymorphonuclear leucocytes. In such areas the tubules may be either dilated or collapsed; their epithelium may be flat, cylindrical, or vacuolated, and occasionally regenerative processes may be seen (Fig. 3). The glomeruli, likewise, are implicated. The tufts are swollen and fill the capsular space. The capsules themselves are delicate. The tufts show

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occasional extensive hyaline thrombi (Fig. 4) and intercapillary as well as capsular adhesions. Occasionally red blood cells or polymorphonuclear leucocytes may be found in the capsular space. In these scarred areas the finer architecture of the kidney is obscured, whereas between the scars changes of interstitial tissue, tubules and glomeruli are not remarkable.

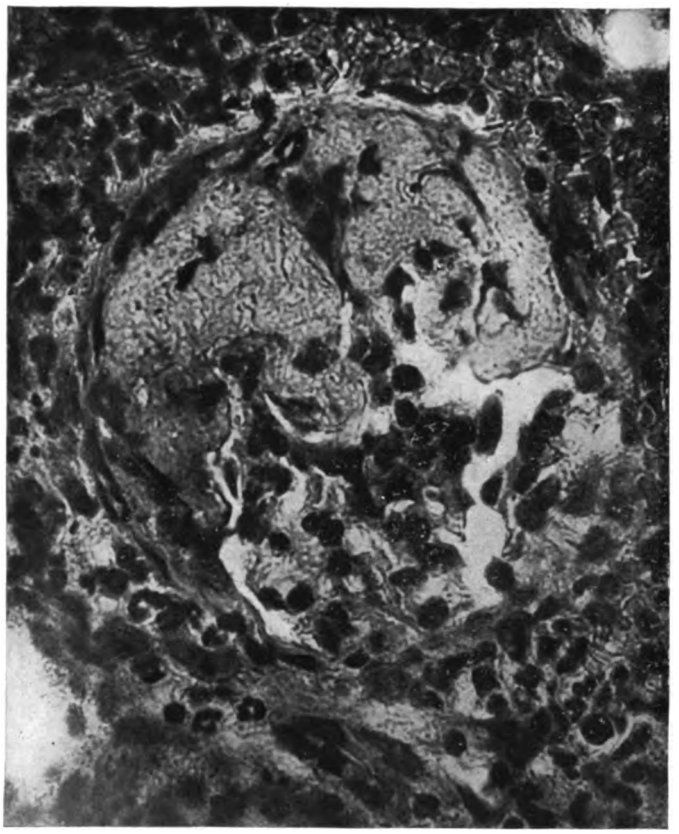

FIG. 4.

The important points in the history of the animal subsequent to the second laparotomy are indicated in Chart I.

On April 26, 38 days after the original injection of *B. bronchisepticus* into the right renal artery and three weeks after the removal of the left kidney, the animal was anesthetized and a small wedge of the right kidney was excised. It showed the following histological picture:

The capsule is thickened, but otherwise shows no evidence of active inflammatory process. Extending into and scattered through the cortex,

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are occasional typical scarred areas where the interstitial tissue is increased and studded with small mononuclear cells. Here the tubules are atrophied or dilated, and lined with a low cubical epithelium. They may contain casts. The glomeruli are numerous in these scars; they vary greatly in size and show capsular adhesions, and early hyalinization. The

FIG. 5.

remainder of the kidney cortex including the blood-vessels presents no definite change (Fig. 5).

The general condition of the animal and the urinary findings immediately after the fourth operation are presented in Chart II.

During the next two months the dog was given systematic daily exercise on a treadmill. He remained in excellent condition. The urine showed either no albumin or only traces; rarely an occasional cast.

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CHART I.—DOG 27.

Date.	Amt. c. c.	Urine. Sp. gr.	Urine. Alb. gm. per l.	Urine. Mic. exam.	Remarks.
Mar. 25	.....	.....	.....	.....	Looks well but does not eat.
" 29	340	1,022	0.25	.....	Has made a good recovery.
" 30	450	1,030	0.5	.....	
" 31	450	1,030	0.25	.....	
Apr. 1	400	1,040	.....	.....	
" 2	420	1,040	.....	.....	
" 3	250	1,020	.....	.....	
" 4	200	1,032	.....	.....	
" 5	450*	1,032	0.25	Neg.....	Animal is in excellent condition.
" 6	.....	.....	.....	.....	Has made an excellent recovery.
" 7	400	1,020	Trace.	.....	Phenolsulphonephthalein output 30% in 1 hr. Blood urea 22 mg. per 100 c. c.
" 8	350	1,028	0.25	.....	
" 9	450	1,032	.....	.....	
" 10	440	1,034	.....	.....	
" 11	240	1,036	0.25	Casts, pus, few mononuclear cells.	Blood urea 30 mg. per 100 c. c.
" 12	350	1,040	.....	.....	
" 13	460	1,030	0.25	.....	Phenolsulphonephthalein output 52% in 1 hr. Blood urea 25 mg. per 100 cc.
" 14	450	1,020	Trace.	.....	
" 15	450	1,020	.....	.....	
" 16	250	1,030	.....	.....	
" 17	450	1,030	.....	.....	
" 18	150	1,030	.....	.....	
" 19	400	1,040	0.25	.....	Phenolsulphonephthalein output 50% in 1 hr. Blood urea 27 mg. per 100 c. c.
" 20	600	1,021	.....	.....	
" 21	650	1,022	.....	.....	
" 23	220	1,040	.....	.....	
" 24	200	1,040	.....	.....	
" 25	140	1,040	.....	.....	
" 26	.....	.....	.....	.....	Mean blood pressure is 120 mm. Hg.

*Third operation; under ether anesthesia the left kidney was removed through a lumbar incision.

On July 27, about four and one-half months after the original injection of *B. bronchisepticus* into one kidney and more than three months after total removal of the uninjected kidney, the mean blood pressure was 140 mm. Hg.; the phenolsulphonephthalein excretion 49 per cent in one hour; the blood urea 48 mg. per 100 c. c.

Discussion.—The above protocol is representative of a group of older dogs, in which no demonstrable general infection occurs after the

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injection of *B. bronchisepticus* into a renal artery. The kidney, however, shows immediate acute focal inflammatory lesions, which rapidly subside and result in focal scars similar to those that are frequently encountered both in the canine and human kidney. These latter lesions are associated with an intermittent albuminuria and cylinduria which persist for months, although there are no other evidences of renal insufficiency.

CHART II.—DOG 27.

Date.	Amt. c. c.	Urine.		Mic. exam.	Remarks.
		Sp. gr.	Alb. gm per l.		
Mar. 26	340	1,054	.....	.....	
" 27	440	1,020	.....	.....	Excellent recovery.
" 28	250	1,030	0.5	.....	
" 29	300	1,042	.....	.....	Phenolsulphonephthalein output 46% in 1 hr. Blood urea 30 mg. per 100 c. c.
" 30	410	1,034	.....	.....	
May 1	440	1,034	.....	.....	
" 19	.....	.....	0.25	Pus, no casts, a rare renal cell.	Phenolsulphonephthalein output 69% in 1 hr. Animal very well.
" 22	450	1,050	.....	.....	
" 23	350	1,030	.....	.....	
" 24	440	1,032	.....	.....	

GROUP II.

Animals That Died Acutely with Fulminating Renal Lesion and an Acute General Reaction.

Illustrative Case.—Dog 17. Large young male. Feb. 29, 1916. Under ether anesthesia a laparotomy was performed and 5 c. c. of a milk culture of *B. bronchisepticus* injected into the right renal artery. Immediately after the injection and release of the arterial circulation the organ became unusually tense and firm and the needle puncture in the arterial wall bled considerably.

The next day the blood urea was 122 mg. per 100 c. c. The animal developed diarrhea, anorexia, and oliguria; death occurred on the sixth day after injection.

Autopsy.—The right kidney is at least larger by one-half than the left (Figs. 6 and 7). Its capsule is not adherent, though somewhat thickened and suffused with blood. The surface of the organ is brownish purple, thickly mottled with yellowish, raised areas from 1 to 2 mm. in diameter On section the kidney is purplish red, engorged with blood, and with all the normal markings obscured. No evident abscesses are present. Cortex

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and medulla seem to share equally in the increase in size of the kidney. The rest of the organs present nothing remarkable.

Under the microscope are masses of red or white blood cells scattered through fairly well-preserved kidney tissue. · The interstitial tissue is spread by engorged vessels, edema and cellular accumulations. In many

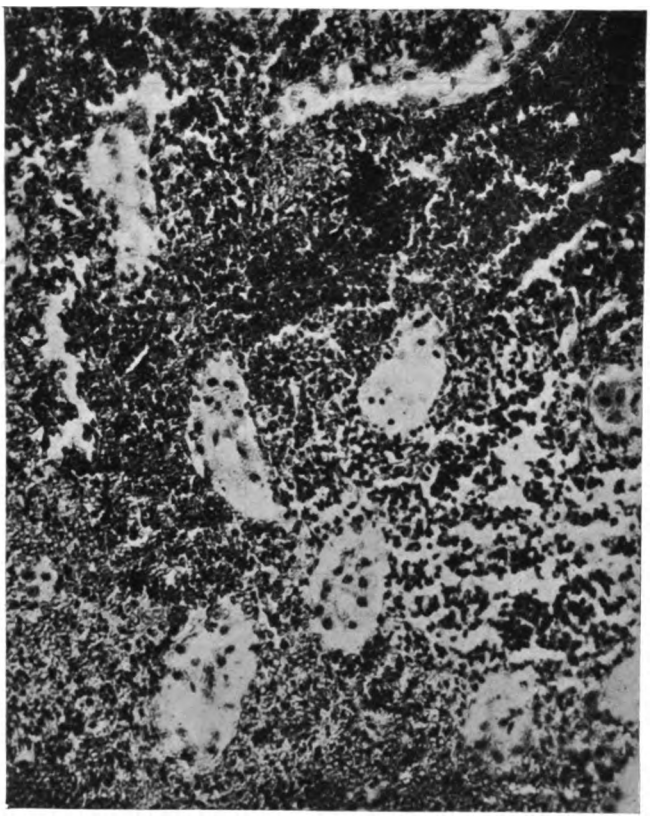

FIG. 8.

places the exudate is composed almost entirely of red cells; in others of polymorphonuclear leucocytes. These areas give the section a mottled appearance (Fig. 8). In the areas of greatest engorgement the architecture of the kidney is lost. Collapsed or nearly collapsed tubules, lined with low epithelium, streak the mass of red and white cells. The tubules themselves contain in these places small clumps of cellular detritus. Where the tubules are better preserved, a similar exudate occurs in the interstitial

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tissue to a lesser extent. The tubular epithelium shows acute and vacuolar degeneration. The glomeruli are implicated in most instances. They may show simply a compression, but as a rule emboli occur, associated with necrosis of part (Fig. 9) or all of the tuft, and even with miliary abscess formation (Fig. 10). Where the process is less marked in the tuft, a wedge

FIG. 9.

of necrotic capillaries appears to be plastered to the capsule. The capsular space may contain red blood cells and polymorphonuclear leucocytes. The capsule itself, except where it is in contact with the diseased tuft, is not implicated. The large blood-vessels are obscured by the extensive exudative process. In the pyramids the collecting tubules contain hyaline casts, cellular detritus, red blood cells and polymorphonuclear leucocytes.

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Sections of the uninjected kidney and of other viscera show only an extreme degree of cloudy swelling.

Discussion.—The above protocol is descriptive of a large group of young animals, in which the injection was followed by a fulminating acute non-suppurative infiltration process. It is probably focal in

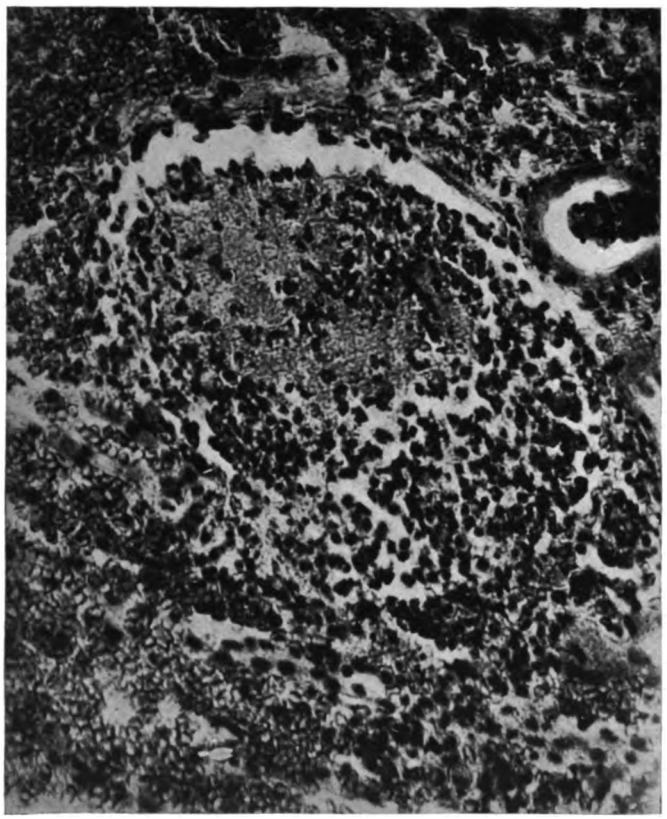

FIG. 10.

nature, but the foci are so large and so numerous that the intermediate areas are only demarcated by a slightly less intense involvement. Such lesions are rare in human pathology, but they find their analogy in occasional cases of acute septicæmia with or without cardiac valvular implication.

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GROUP III.

Animals with a Milder Renal Lesion Which Progressed After the Less Severe General Reaction Had Subsided.

Illustrative Case.—Dog 25. March 10, 1916. Under ether anesthesia a laparotomy was performed and 5 c. c. of a milk culture of *B. bronchisepticus* were injected into the right renal artery. The animal recovered from the operation promptly. It was drowsy and ate little for several days, but after these mild general signs had disappeared, the urine continued abnormal as indicated in Chart III.

CHART III.—DOG 25.

Date.	Amt. c. c.	Urine.		Mic. exam.	Remarks.
		Sp. gr.	Alb. gm. per l.		
Mar. 16	260	.....	2.0	Many epithelial cells.	
" 18	330	1,022	2.0	Casts; few small round cells.	
" 19	450	1,018	.....	.....	
" 20	250	1,022	0.5	No casts seen...	
" 21	370	1,020	0.5	.....	Phenolsulphonephthalein excretion 40% in 1 hr. Blood urea 100 gm. per 100 c. c.
" 22	660	1,012	2.0	.....	Ether anesthesia, laparotomy. The left kidney was found normal. Its lower pole was resected. The right kidney was definitely enlarged and of much firmer consistence than normal. The surface was somewhat mottled.
" 23	100	1,032	6.0	Casts, blood, and small round cells.	General condition good. Wound healing well.
" 25	450	1,012	0.5		
" 26	350	1,016	.....		
" 27	200	1,030	2.0		
" 28	250	1,022	1.0		

The animal was lively and seemed well. Although he ate abundantly there was definite loss of weight. On March 28 under paraldehyde anesthesia (1.7 c. c. per kilo of body-weight) each ureter was exposed and cannulated. The outflow of urine from the left kidney in one hour was 45 c. c. and contained 17 per cent phenolsulphonephthalein; from the right the flow was 15 c. c. and contained only traces of the dye.

During the night the dog died, not having definitely recovered from the anesthetic and operation.

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Autopsy.—The right kidney is not markedly decreased in size (Fig. 11); the capsule is thickened and adherent. The surface is slightly granular and pale reddish brown. On section the cortex is slightly narrowed; its striations are obscured. The pyramids are paler than the cortex. The pelvis is normal. The remainder of the autopsy reveals no noteworthy changes.

On microscopic examination there is no appreciable difference between specimens removed 12 days after injection and those of the autopsy which was made on the 18th day. The capsule is irregularly thickened by fibrous tissue which shows no evidence of active inflammatory process. The cortex of the kidney has been greatly changed by an infiltration of mononuclear cells throughout the interstitial tissue (Fig. 12). This infiltration is not uniform. In many places it forms dense masses which compress and obscure the tubular parenchyma. These tubules contain casts and occasional masses of necrotic cells, but almost always retain a low, cubical, well-preserved epithelium. Where the tubules are not so markedly compressed, they also contain foreign elements in their lumina, and a higher vacuolated epithelium which, in many places, shows regenerative mitosis (Fig. 13).

Throughout the cortex the glomeruli are very conspicuous. They are all enlarged, relatively acellular and stain pale pink, in contrast to the deep blue-streaked cortex. They contain little blood. The glomerular capsule is surrounded by mononuclear cells similar to those in the remainder of the interstitial tissue. Otherwise the capsule is delicate. The glomerular spaces are usually well defined and many contain occasional blood cells, polymorphonuclear leucocytes, or serum. The glomerular tuft in many places shows hyalinization and accumulation of polymorphonuclear leucocytes. Furthermore, adhesions between tuft and capsule occur, although not very frequently (Fig. 14). The large blood-vessels show a definite thickening of the walls, which apparently involves both intima and media, although the latter to a more marked degree (Fig. 15). The left uninjected kidney shows a few areas of interstitial infiltration with small mononuclear cells.

The above experiment approximates in its histological results more nearly the chronic progressive renal lesion occurring spontaneously in the dog. However, since this animal was sacrificed in the attempt to study the differential function of the two kidneys, a second case of the group may be presented to illustrate more clearly the progressive nature of the lesion.

GROUP III.

ILLUSTRATIVE CASE No. II.—Dog No. 19. On March 1, 1916, under ether anesthesia a laparotomy was performed and 5 c. c. of a milk culture of *B. bronchisepticus* were injected into the right renal artery. During the subsequent week the animal seemed entirely well. The urine contained a

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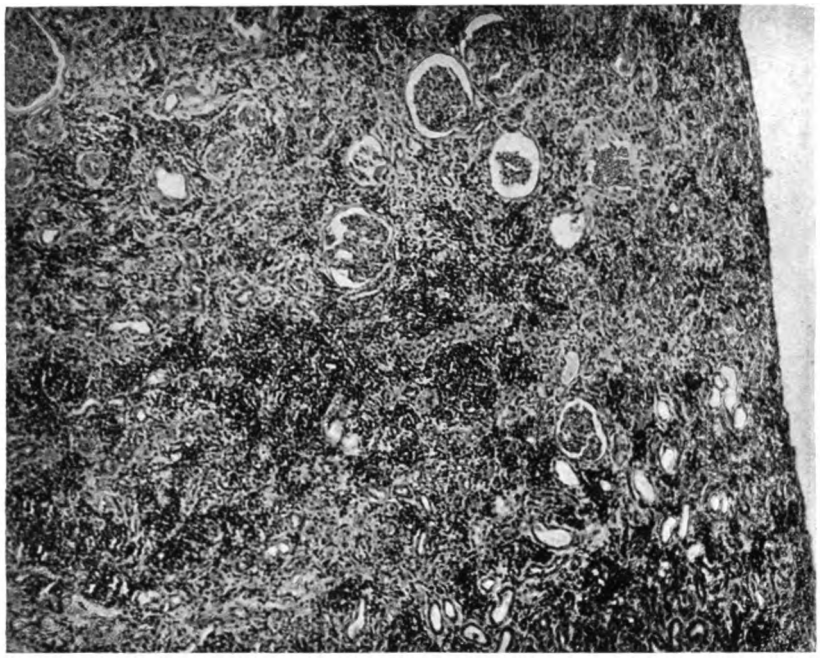

FIG. 12.

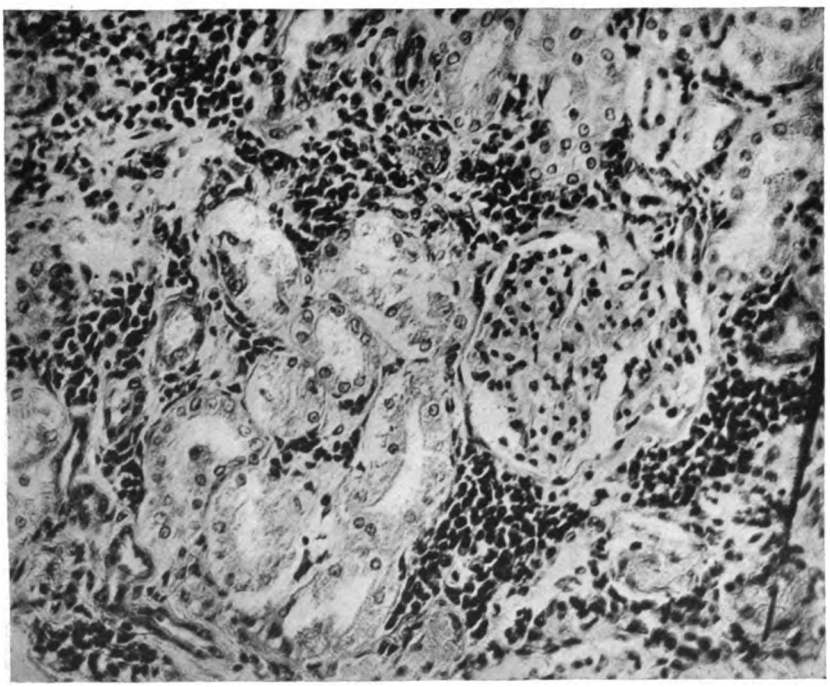

FIG. 13.

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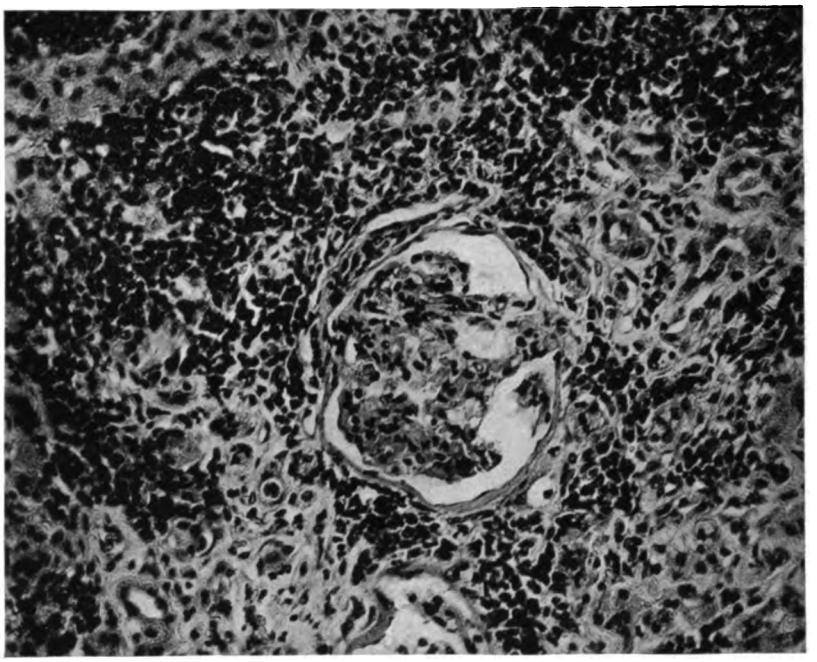

FIG. 14.

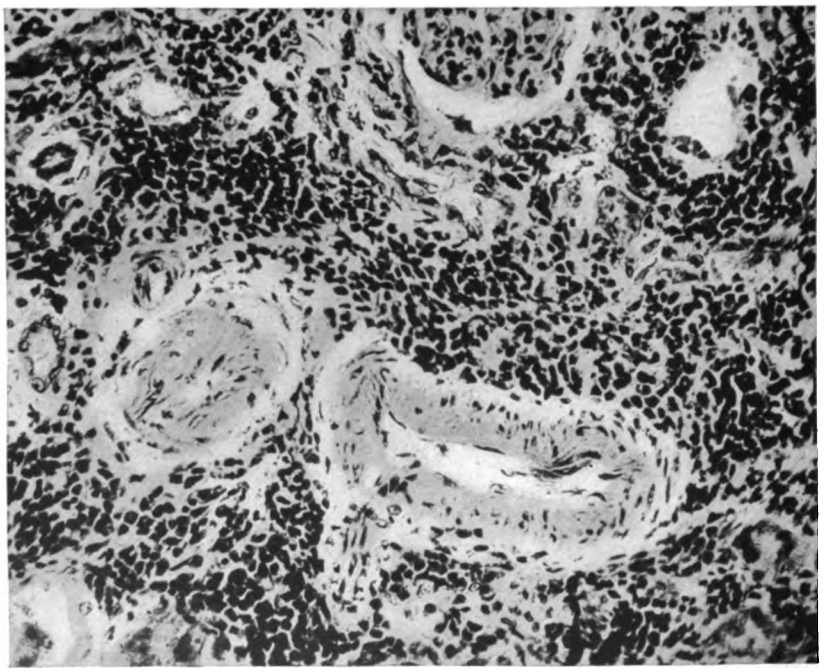

FIG. 15.

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slight trace of albumin; the phenolsulphonephthalein output in one hour was 50 per cent.

A second laparotomy on March 9 showed the right kidney surrounded by rather numerous adhesions which bound it to the tail of the pancreas. It was somewhat enlarged, and its surface was deep red, with fine yellowish mottlings. A small wedge was excised for microscopic examination.

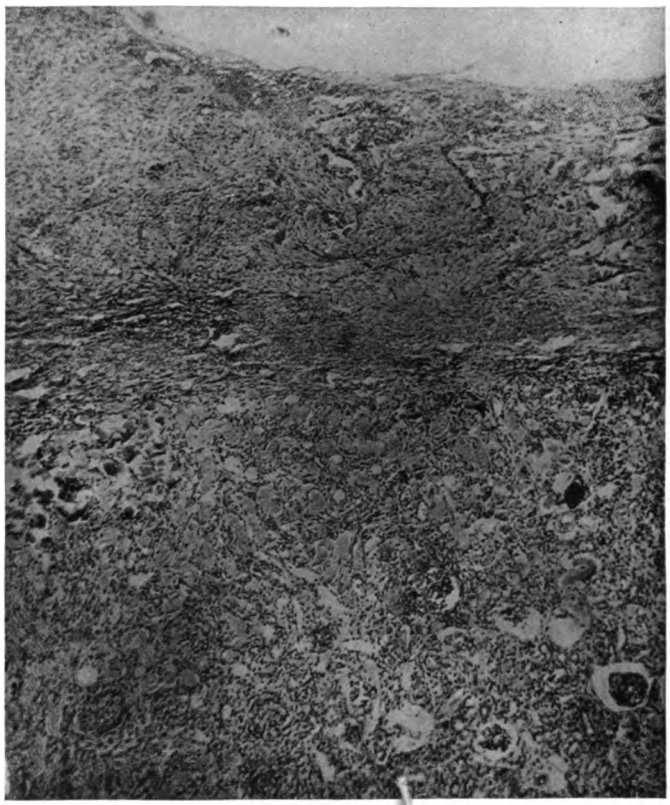

FIG. 1[illegible].

Microscopic Section of Kidney Nine Days After Injection.—The capsule is irregularly thickened by vascular granulation tissue. The cortex of the kidney is uniformly changed. The interstitial tissue is increased and appears as a loose, young, connective-tissue stroma, which does not compress the parenchyma of the cortex to any extent (Fig. 16). The tubules are indistinctly made out on account of the very extensive epithelial necrosis which has everywhere taken place. In most instances the epithe-

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lium of the convoluted tubules lies free within the lumen, and appears as a pale, pink-staining cast. There is, however, a low epithelium to be seen in the collecting tubules and evidence of extensive degeneration in the convoluted tubules (Fig. 17). The glomeruli vary greatly in appearance. Many of them show extensive vacuolization, the walls of the tuft being spread wide apart and in many places plastered to the capsule.

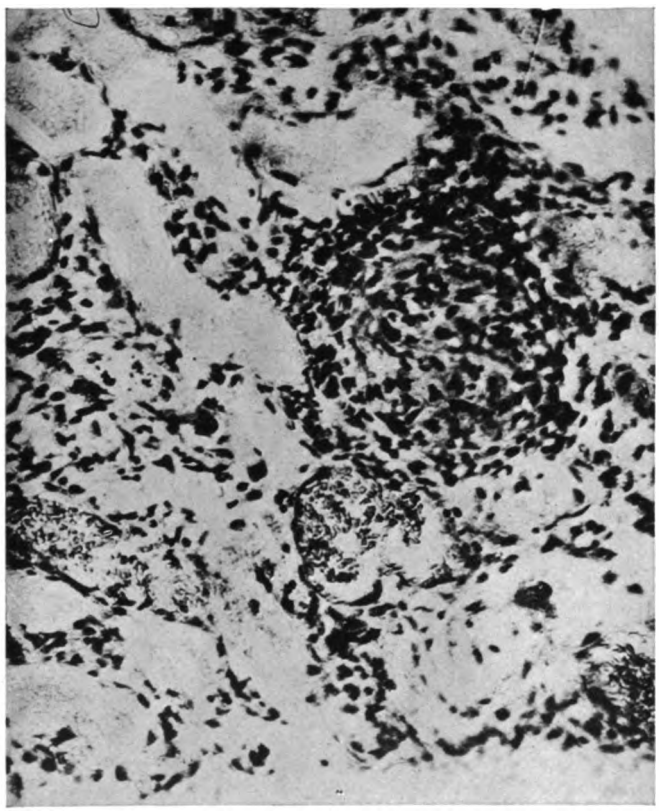

FIG. 17.

Others show marked increase and swelling in the cellular elements of the tuft. Still others are engorged, and cells, as well as serum, may fill the glomerular space (Fig. 18). The glomerular capsules are implicated in a process similar to that described in the interstitial tissue elsewhere. They show a slight increase of loose connective tissue at their peripheries. There are no marked changes in the blood-vessels.

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The animal recovered rapidly from this second operation. On March 15 the urine contained only the slightest trace of albumin; the sediment was negative.

Chart IV indicates the further progress of the disease.

CHART IV.—DOG 19.

Date.	Amt. c. c.	Urine.		Mic. exam.	Remarks.
		Sp. gr.	Alb. gm. per l.		
Mar. 18	220	1,042	0.5	.....	
" 19	260	1,040	4.0	.....	
" 20	250	1,035	1.0	Many casts....	
" 21	120	1,035	0.25	Occasional cast.	
" 22	40(?)	1,045	4.0	.....	Phenolsulphonephthalein output 50% in 1 hr. Blood urea 48 mg. per 100 c. c. Animal has marked general infection and is sick.
" 23	150	1,020	2.0	.....	
" 24	140	1,038	1.5	Occasional cast.	Animal is better, but does not eat.
" 25	110	1,040	1.5	.....	
" 26	200	1,035	0.5	.....	
" 28	140	1,020	0.25	.....	Much better; eats and walks strongly. Nose and eyes are almost clear.
" 29	450	1,010	Trace.	.....	
" 30	460	1,010	0.25	.....	
" 31	450	1,010	.....	.....	
Apr. 4	450	1,008	Trace.	.....	
" 6	420	1,012	0.25	.....	
" 7	450	1,012	0.25	.....	Operation—left nephrectomy.
" 8	200	1,010	.....	.....	
" 9	140	1,012	.....	.....	
" 10	150	1,012	.....	.....	
" 11	290	1,012	0.5	Few casts; much pus. Occasional epithelial cells.	Phenolsulphonephthalein output a trace in 1 hr. Blood urea 114 mg. per 100 c. c.
" 12	140	1,018	.....	....	
" 13	260	1,022	0.5	.....	Phenolsulphonephthalein output a trace in 1 hr. Blood urea 186 mg. per 100 c. c.
" 14	.....	.....	.....	.....	Vomits. Urine cloudy. Blood urea 359 mg. per 100 c. c.
" 15	75	1,017	2.0	.....	
" 17	250	1,010	2.0	.....	Vomits, drowsy, condition poor.
" 18	.....	.....	.....	.....	Blood urea 348 mg. per 100 c. c. Death.

Autopsy.—All the organs are normal except the right kidney which is surrounded by some adhesions; it is small and shrunken in appearance and weighs only 6.5 gm. (Fig. 19). There is no evident cardiac hypertrophy.

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Microscopic Examination of the Kidney Removed at Autopsy 50 Days After Injection.—The entire capsule is thickened with fibrous tissue. The cortex is irregularly involved by the chronic inflammatory process (Fig. 20). In the areas most markedly implicated the fibrous tissue is dense and has caused an almost complete disappearance of the tubules. Most of them have minute lumina and a very low epithelium. They contain

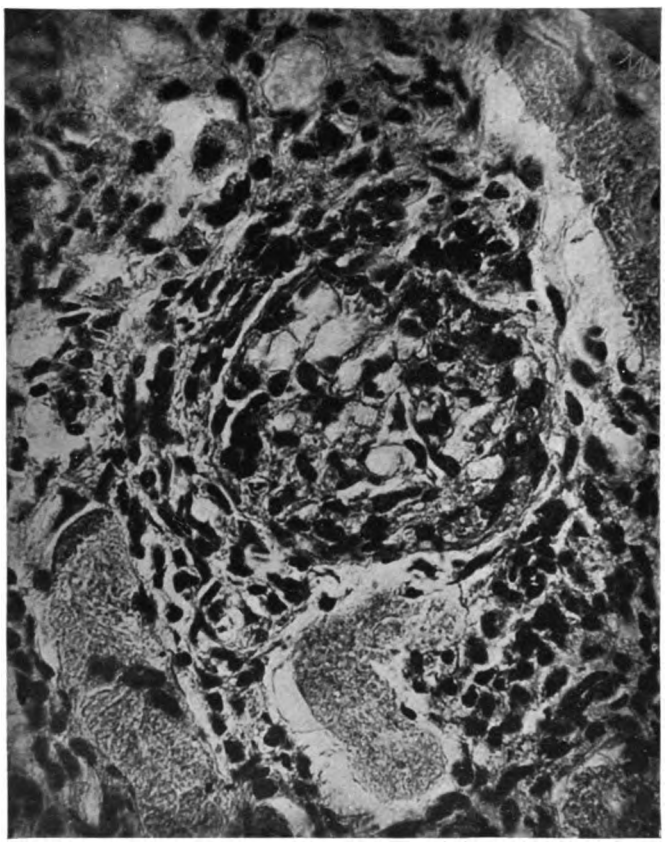

FIG. 18.

homogeneous casts. In neighboring areas the tubules are definitely enlarged, lined with a similar low epithelium and have very large lumina containing a pink-staining, albuminous material. In these more extensively scarred areas the glomeruli are still abundant and conspicuous on account of absence of the tubules. They vary from very small ones to those several times the normal size, and show all stages of necrosis, healing

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with adhesion formation and hyalinization (Fig. 21). The blood-vessels in these densely scarred areas have somewhat thickened walls, although this is not conspicuous. In nearby areas the changes are less extensive, but have the same general characteristics. The tubules in particular are of interest on account of their increased size and the very high, extensively vacuolated epithelium which lines them.

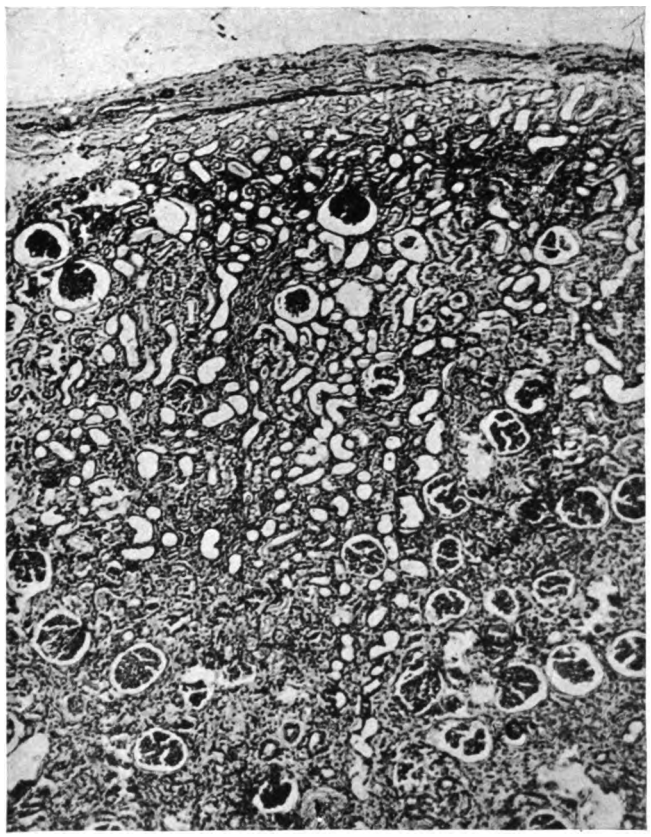

FIG. 20.

The uninjected kidney, removed 38 days after the original operation, shows an occasional area of small-round-cell infiltration in the interstitial tissue with an associated dilation of the tubules and an atrophy of their lining epithelium. These extend along the course of the blood-vessels, which have somewhat thickened walls. No glomerular changes are to be seen.

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Discussion.—The above two protocols of Group III are characteristic of the changes found in a number of animals subsequent to the injection of *B. bronchisepticus* into the renal artery. The definite evidences of general infection were associated with and followed by acute renal

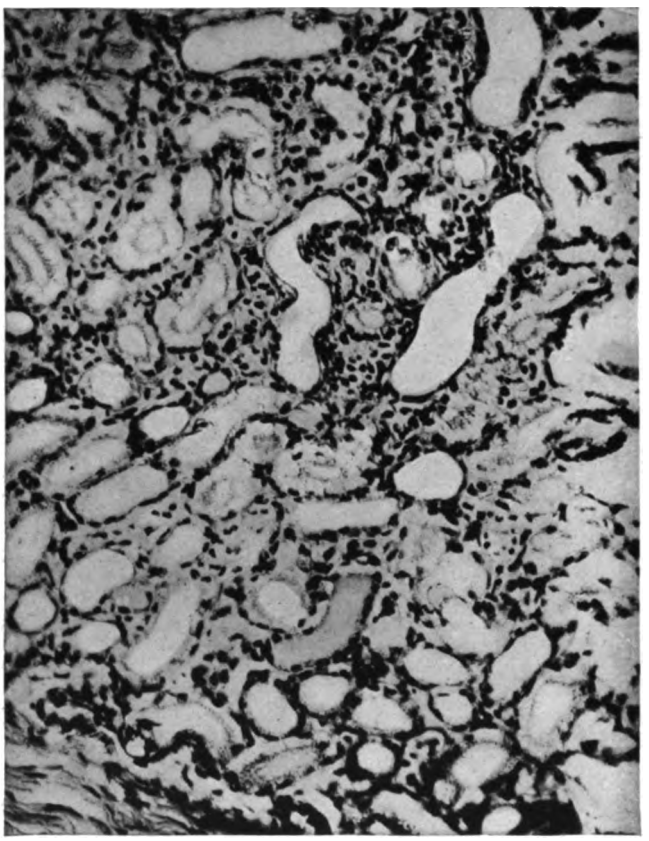

FIG. 21.

changes, which in part subsided, with resultant gross and histological changes typical of those found spontaneously in the dog and in the better known small granular kidney of chronic diffuse nephritis in man.

The initial acute changes in the kidney were so severe that they resulted in rapid and extensive anatomical alteration of the renal

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cortex, together with impairment of its function, so that death from renal insufficiency occurred shortly after the removal of the uninvolved kidney.

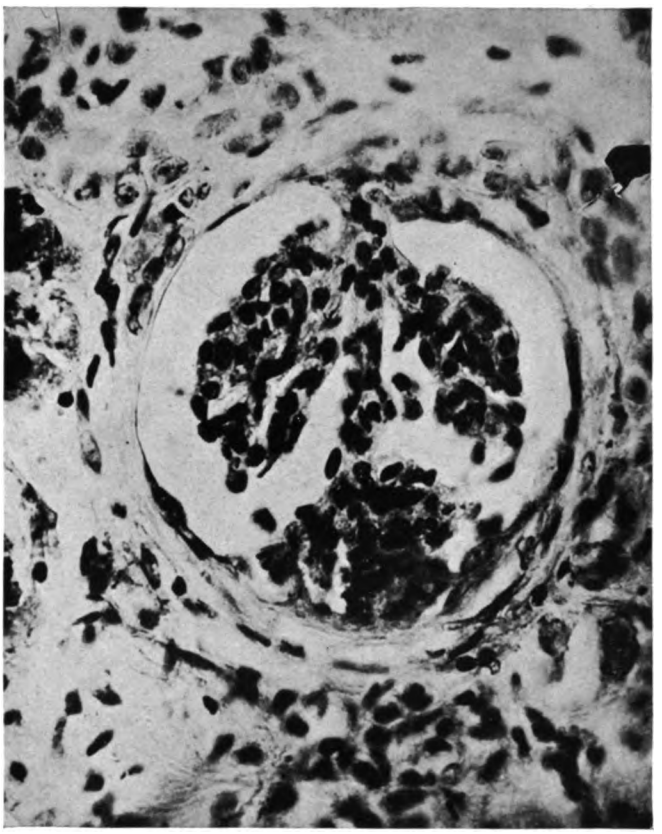

FIG. 22.

CONCLUSIONS.

Spontaneous renal lesions similar even in detail to those found in the human kidney in the progressive, non-suppurative types of nephritis occur in dogs.

Similar conditions may be experimentally produced by the injection of the *B. bronchisepticus* into the renal artery of dogs.

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The results of this injection vary, but the animals tend to group themselves as follows:

1. Those in which no demonstrable general infection occurs; the kidney, however, shows immediate acute inflammatory lesions which rapidly subside and result in focal scars associated with intermittent albuminuria and cylinduria.

2. Those that died acutely with a fulminating renal lesion and an acute general infection.

3. Those in which there was definite evidence of general infection as well as renal involvement. The first subsided, while the kidney changes progressed and led so rapidly to functional impairment that the organ was unable to maintain its efficiency after the other kidney had been removed.

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MESARTERITIS OF THE PULMONARY ARTERY.

By M. C. WINTERNITZ and H. C. SCHMEISSER.

(From the Department of Pathology of The Johns Hopkins University, Baltimore.)

Mesarteritis, so frequent in the thoracic aorta, is exceptionally rare in other large vessels. It occurs in the abdominal aorta, and isolated examples of similar implication of the iliac, femoral, splenic, pulmonary and other arteries have been recorded. The recognition of the specificity of mesarteritis, its etiology, its differentiation from other types of aortic disease, and its relation to aneurysm formation, though slow, has now become almost general.

In the pulmonary artery, as in the aorta, the lesion is distinct from other types of atherosclerosis. On account of its rarity, however, the significance of pulmonary mesarteritis can be appreciated only by a consideration of the analogous lesion in the aorta. For a clearer conception of the process, therefore, pulmonary atherosclerosis and mesarteritis will be briefly discussed before some of the instances of syphilis of the pulmonary artery in the literature and two new observations are presented.

Pulmonary Atherosclerosis.

1. *Pathological Anatomy.*—Moderate grades of pulmonary atherosclerosis are frequent enough at the post-mortem table. It appears as yellowish or yellowish-white plaques or nodules varying in size, and more or less elevated after the vessel is incised. Calcification occurs to a slight degree. The vessel wall may be thickened, its elasticity lost, and the main stem considerably dilated. Atheromatous ulcers have not been described (Torhorst,[1] Thorel,[2] Fischer,[3] Posselt,[4] and others).

Histologically, the lesions are similar to those of general arteriosclerosis. The essential changes are a primary thickening of the intima and a subsequent degeneration. Brunning's[5] idea that the lesion involves primarily the elastico-muscular layer seems to have been disproved, and recent writers (Torhorst, Fischer) do not agree with Thoma as regards the pulmonary artery at least, that the primary degeneration involves the media. This is only one of the points in dis-

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pute. They are many, and correspond naturally to similar ones that have arisen in the literature of general arteriosclerosis.

Primary medial changes, either of the muscle or elastic tissue, are not described, nor are blood-vessel formation or other granulation-tissue products found in association with the much thickened and degenerated intima. In the larger vessels alone, isolated degenerations, involving, however, only the elastic connective-tissue ground-substance, occur and seem most likely to appear where the media has not received sufficient protection by intimal thickening. The media may be thinned, not only relatively but absolutely, beneath large intimal plaques.

2. *Incidence.*—Minor histological changes in both intima and media are described by Torhorst, where grossly there was no visible lesion. More marked processes are not infrequently found where there is a general atherosclerosis. As Fischer points out, however, the blood pressure in the pulmonary tree is to a great extent independent of that in the systemic vessels, and in these cases the high blood pressure, an important factor in the genesis of arteriosclerosis, may be lacking. Furthermore, the most severe atherosclerotic changes in the pulmonary artery occur in pulmonary emphysema, cardiac disease, especially mitral stenosis and other conditions associated with a long-continued, increased blood pressure in the lesser circulation.

Even in this group of cases, however, the pulmonary sclerosis does not influence the clinical picture in any way, and anatomically it is simply an interesting, casual finding. There are, however, according to Monckeberg,[4] rare instances in the literature in which sclerosis of the pulmonary artery occupies the foreground of the picture, in which it stands alone responsible for the clinical and anatomical findings.

Monckeberg was able to find only two such cases, those of Romberg[5] and Aust,[6] when he described his own two in 1907. Three of the four cases occurred in young individuals. Dyspnœa, cyanosis, cardiac enlargement, œdema and chronic passive congestion were foremost in the clinical picture. At autopsy, the heart valves were normal, and there was a marked hypertrophy of the right ventricle, without corresponding lesions in the lungs to account for the change. The pulmonary artery was dilated throughout its stem and main branches, and then markedly narrowed in the finer branches. The intima of the rigid vessel wall was covered with thick, plaque-like yellow patches, which, in Monckeberg's cases were similar histologically to the usual extensive atherosclerotic processes.

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Very probably some of the cases reported in 1908 by Rogers [9] from Bengal, although the evidence is not conclusive, should be included in this group. More recently still, Sanders [10] has added a typical case. The subject has been reviewed by Posselt, who is inclined to explain the original cases of Romberg and Aust on the basis of a congenital narrowing of the cardiac ends of the pulmonary vein.

Mesaortitis.

The etiology of these atherosclerotic processes in the pulmonary artery, as of those in the systemic vessels, is very imperfectly understood (see Posselt). Until recently syphilis was believed to be an important predisposing factor for general atherosclerosis, but the work of Doehle [11] and Heller [12] inaugurated the present conception that syphilis produces a specific process in the blood-vessels distinct from other types of arterial disease. This lesion is localized almost exclusively in the thoracic aorta. Macroscopically, it is characterized as much by the lack of ulceration and calcification as by the thickening of the vessel wall, its loss of elasticity and the linear radiating contractures of the intima, which not infrequently enlarge to form irregular depressions and aneurysms. Microscopically, in contrast to what is found in the usual atherosclerotic processes, the seat of the lesion is in the outer two coats of the vessel. It consists of widespread, round-cell infiltration of the adventitia around the vasa vasorum, but above all, by the replacement of the elastic fibers in the media by granulation tissue very rich in round cells, or of hyaline fibrous tissue that later replaces this granulation tissue. The intima may remain normal, and the oft-found thickening is either secondary or a complication with a pure atherosclerotic process, to which the vessel, made inelastic by the medial disease, seems particularly prone.

As distinctive as are the anatomical characteristics of mesaortitis, their relation to syphilis has been more difficult to determine. Herxheimer,[13] in 1907, reviewed this question and cited equally important positive and negative evidence. To the latter belongs Ziegler's opinion that similar changes also occur in coccus and other infections. Herxheimer concludes that it is only possible to include the rare gummatous arteritis as of unquestionable syphilitic origin and, although a large number of the pure "Schwielige Sclerosen" undoubtedly should be included in this etiology, it is not possible in the individual case to come to a definite conclusion, inasmuch as the scar presents nothing

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characteristic. This conservatism became modified very decidedly during the next eight years, as is evidenced by the tone of Thorel's[8] review. The spirocheta pallida has been demonstrated in the necrotic areas of the vessel wall only in a few instances, but with the help of the Wassermann reaction it has been shown that a large percentage of the lesions occur in individuals infected with syphilis (75.9 to 94 per cent). A positive reaction does not indicate that a specific organic lesion is necessarily due to syphilis; nevertheless, its coincidence with aneurysm, tabes and general paralysis, and the other known lesions of syphilis, has strengthened the opinion that mesaortitis is brought about in the first instance by the luetic virus.

The rapid change in the conception of the etiology of the lesion in the aorta is in large part due to the frequency of its occurrence. It is more common than severe arteriosclerosis (Benda[44], Thorel[8]). It was found in 6.89 per cent of 1436 autopsies and occupied the third place after tuberculosis and malignant disease in Oberndorfer's studies.

Still, as Thorel points out, the macroscopic and microscopic appearances, in the majority of cases, are in themselves not specific for syphilis. They do not differentiate themselves, as a rule, in any way from other inflammatory processes, as they are observed also in other regions. Even the presence of giant cells in the occasional necrotic areas are not universally accepted as indices of their gummatous nature.

In large vessels, other than the aorta, on the other hand, mesarteritis is rare. Herxheimer includes a few cases in his review (p. 205).

As has been said, the usual types of atherosclerosis of the pulmonary artery are similar to those found elsewhere in the body, and they differ sharply from those changes which are, in all probability, brought about by syphilis. At present, syphilis is not believed to play a rôle in the genesis of these general atherosclerotic processes. If syphilis involves the pulmonary artery, it is just to assume that the lesions will be similar to the specific lesions in the aorta.

The most conclusive evidence of the specificity of a lesion in the pulmonary artery would be the demonstration of the spirocheta pallida. This can hardly be expected as, in spite of the very great frequency of mesarteritis of the aorta, the organism has only been found in the diseased vessel wall in a very few instances. Less satisfactory but important criteria would be firstly the presence of gummata in the wall of the vessel and then of a typical mesarteritis.

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Literature.—The entire literature on the subject of syphilis of the pulmonary artery is small; many of the cases were reported before the etiology of syphilis and the Wassermann reaction became known, and in many the description of the anatomical changes is too meager to allow of definite deductions.

Nevertheless, a number of definite cases of gumma of the pulmonary artery with or without an associated mesarteritis and of mesarteritis alone have been described:

GROUP I.

GUMMATA OF THE PULMONARY ARTERY.

A girl,* 21 years old, who had been treated for definite secondary syphilis showed at autopsy gummata of the skull, scars and gummata of the liver and stenosis of the lower branch of the right pulmonary artery. This stenosis extended over a distance of one inch and within this area there was a nodule the size of a bean (.75 cm. x 2.5 mm.) which projected into the lumen of the vessel. The nodule arose in the media, was covered with intact intima and was composed of a granulation tissue similar to that at the periphery of the liver gummata. The media, furthermore, was thickened for a considerable distance toward the lung and caused a definite narrowing of the vessel.

A man,† aged 31 years, who had suffered for eight years with constitutional syphilis, showed at autopsy gummata of the pectoralis major muscle, tongue, skull and heart muscle. In the pulmonary artery, between two valves there was a nodule the size of a pea and many smaller ones. On section these were reddish grey, soft and homogeneous. On the wall of the pulmonary artery, just above the left cusp, there was a small diverticulum one and one-half inches wide in which similar small nodules occurred. The pulmonary valves were normal, the artery wall was thickened and adherent to the surrounding structures. Similar small nodules, the size of coffee beans, were found in the left main branch of the vessel.

A woman,‡ aged 32 years, with a history of breathlessness and fainting attacks showed clinically a mitral systolic murmur and heart-block. At autopsy the left lung was retracted; the heart weighed 640 gm. The right side was dilated and hypertrophied; the left ventricle was slightly dilated. Gummata of the interventricular septum and of the wall of the pulmonary artery just above the pulmonary valves were the only lesions of syphilis found in the body. The brain was not examined.

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* O. Weber. Verh. d Niederrh. Ges., 1863, p. 171. Med. Centralz. 1836, Nr. 103; cited by E. Wagner, Arch. der Heilkunde, 1866, VII, 530.

† E. Wagner. Arch. der Heilkunde, 1866, VII, 530.

‡ H. Hanford. British Medical Journal, 1904, II, 1745.

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A man,* aged 37 years, who had died suddenly, showed at autopsy a tumor in the wall of the pulmonary artery just above the semilunar valves. It was covered with intima and projected into and narrowed the lumen of the vessel.

Microscopically, it consisted largely of giant cells. The diagnosis lay between a sarcoma and a gumma; the decision was finally in favor of the latter.

The cases of Weber and Wagner are frequently cited and these, with the more recent one of Hanford, undoubtedly belong in this group, whereas that of Sequeira may be questioned.

GROUP II.

Mesarteritis and Gumma of the Pulmonary Artery.

A woman,† 53 years old, had suffered for six weeks from palpitation, dyspnea, edema and cyanosis. A pericardial and an endocardial murmur were made out.

At autopsy in the endocardium of the conus pulmonalis there were three yellowish, soft, elastic nodules, the size of split peas, covered with smooth endocardium. On section they extended into the musculature and had yellow necrotic centers.

The intima, in a defect between two of the pulmonary valves, was thickened. Nearby it was wrinkled in the form of a scar. On both sides of this scar, shimmering through the intima, there were about seven pea-sized or smaller nodules, which on section were similar to those in the ventricle. A similar tiny nodule was found on one of the valve leaflets. The pulmonary artery, which was bound to the aorta by dense fibrous tissue, had a narrowed lumen.

A man,‡ aged 50 years, clinically had edema, increased area of cardiac dulness and other signs of cardiac decompensation.

At autopsy the heart weighed 750 gm. The wall of the pulmonary artery was thickened and the intima uneven. Round or oval nodules, the size of peas, were present in the vessel wall. These varied in consistency; some were soft and dough-like, others tough. On section they showed a cheesy content. The pulmonary valves were adherent to a thickened fold of the pulmonary artery. The wall of the left ventricle measured 1.5 cm. in thickness, that of the right, 1 cm. The endocardium of the right ventricle was thick and opaque. Microscopically, the nodules in the pulmonary artery proved to be gummata.

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* Sequeira. Transact. of the Pathol. Society, 1897, XLVIII, 58; cited by Posselt in Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie. Lubarsch und Ostertag, 1909, 471.

† Schwalbe. Virchow's Arch., 1890, CXIX, 271.

‡ Kasem-Beck. Centralblatt für Innere Medizin, 1900, XXI, 593.

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Kasem-Beck refers to another case reported by him in 1889 (Klin. Zeitung von Botkin).

This was a case of pulmonary stenosis similar to the one above. It differed in so far as the gummata had metamorphosed and contracted scars had resulted. The intima of the pulmonary artery showed scars particularly at the bifurcation; the lumina of the branches were narrowed and the sum of their diameters was less than that of the main stem; they barely admitted the little finger. The walls of the main and smaller branches were thickened and tough. At the bifurcation there was a fibrosis of the adventitia which formed a collar for the main stem and both branches.

A man,* aged 49 years, with a history of untreated syphilis, came under observation with dyspnœa, palpitation, ascites and anasarca.

At autopsy the heart, which was one and a half times the normal size, showed a hypertrophy and dilatation confined almost entirely to the right side. The endocardium of the right ventricle was thickened, particularly at the conus, where there were numerous small nodules that extended into the musculature and on section were yellow with a grey peripheral zone.

The pulmonary artery was markedly dilated—12 cm. in circumference; its walls were irregularly thickened, its intimal surface uneven. On section similar small yellowish nodules were found in the thickened areas.

The left ventricle was slightly dilated and showed a fibrous scar and thrombus at the apex. The intima of the aorta was thickened and a small nodule was found in the septum of the heart below the aortic valve. The lungs were leathery and showed numerous fibrous strands along the vessels and bronchi. The liver showed a dense scar.

Microscopically the pulmonary artery and heart muscle showed areas of granulation-tissue infiltration which merged into typical syphilitic gummata. There was also an endarteritis which had led to complete obliteration of the lumen of many small vessels.

There seems to be no question that all four cases belong to this group. The case of Schwalbe and the first one of Kasem-Beck are frequently referred to; that of Wagner and Quiatowski is recent; it is interesting that the second case of Kasem-Beck has not been included in any review.

GROUP III.

Mesarteritis of the Pulmonary Artery.

Rogers † describes 10 cases of disease of the pulmonary artery. In nine there is no reason to believe that syphilis was the etiological agent. One, however (Case I), is a remarkable example of mesarteritis of the pulmonary artery and valves. It was found in the Museum of the Calcutta Medical College and had been fully described by the late Dr. F. P. McCannell, I. M. S., in the museum catalogue and in the post-mortem register of 1877.

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* Wagner and Quiatkowski. Virchow's Arch., 1903, CLXXI, 369.

† Rogers. Quarterly Journal of Medicine, II, 1908-9, 1.

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The patient was a Hindu male, aged 38 years. He had both a history and scars of a previous syphilis.

The heart was enlarged, particularly the right side. The pulmonary orifice was wide and incompetent; the valves were thickened and deformed. The artery, just above the valve, was dilated to the size of a walnut. Elsewhere it was thickened and leathery, its inner surface rough, opaque and irregularly thickened, corrugated and wrinkled.*

A woman,† 34 years of age, who had had one miscarriage but otherwise no history indicative of syphilis, showed a heart hypertrophied more on the right than the left side. The pulmonary valves were somewhat thickened and all the branches of the pulmonary artery showed plaques of sclerotic change. The wall of the pulmonary artery was thicker than that of the aorta. In addition there was a pulmonary fibrosis that was very marked about the vessels.

Histological evidence was not sufficient to indicate that the changes in the pulmonary vessels were syphilitic, although the author concluded that this was the most probable etiology.

A man,‡ aged 57 years, had always been well until six years before death when he had had a small "stroke." This was followed by difficulty in speech, mental deterioration and paralysis. He had no history of syphilis.

At autopsy there was a bilateral old pachymeningitis.

The left lung was very small and firm. Bands of fibrous tissue extended in from the hilus as far as the thickened pleura. The walls of all the blood-vessels were thickened.

The heart was slightly enlarged, chiefly as a result of hypertrophy of the left ventricle. The pulmonary artery showed an aneurysm of its wall which measured 6 x 3.5 cm. Elsewhere the thickened intima of the main stem of the pulmonary artery showed extensive scarring. The right main branch, which arose near the aneurysm, was very wide. The left was narrowed markedly by dense fibrous tissue which extended between the pulmonary artery and the aorta, but which was only in direct continuity with the former.

The testes showed a fibrous induration.

Microscopically, the pulmonary artery showed a typical mesarteritis; the intrinsic blood-vessels of the lung showed a marked intimal proliferation, a media poor in elastic tissue and a new elastica interna beneath the endothelium. The media and adventitia were not thickened and there was no round-cell infiltration.

A girl,§ 23 years of age, whose father was luetic, but who had not herself

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* The author himself does not emphasize the resemblance of the changes in the pulmonary artery to those in mesaortitis.

† H. Brooks. Proceedings of the New York Pathological Society, 1907. VII, 177.

‡ H. Barth. Frankfurter Ztschr. für Pathologie, 1910, V, 139.

§ Wallis. Hygiea, 1887, p. 59 (29). Cited by Posselt in the Ergebnisse der allg. Path. und path. Anat., Lubarsch und Ostertag, 1909, 471.

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shown any symptoms of syphilis, died several months after the onset of thoracic signs.

At autopsy there was a marked cardiac hypertrophy mainly of the left ventricle. The heart valves were normal. Both the aorta and pulmonary artery showed narrowed lumina and thickened walls. The latter involved the media and adventitia.

Fibrous connective tissue * filled with large gummatous nodules replaced the wall of the arch of the aorta. The stem of the pulmonary artery was indurated and its lumen, just above the pulmonary valves, was definitely narrowed.

A woman,† 42 years old, with no history of syphilis, had a thoracic aneurysm and myocardial insufficiency. At autopsy there was general edema, hypertrophy and dilatation of the right heart and an aneurysm of the pulmonary artery, the size of a hen's egg just above the valves. The vessel above the sac was narrowed for a short distance. The left main branch was dilated; the right was thick-walled and had a small lumen. The wall of the aneurysm was thickened and showed radiating scars but no atheroma or calcification. There was a laminated thrombus on a part of its wall. A dense scar that arose in the adventitia of the pulmonary artery bound together the structures in the anterior mediastinum. Microscopically, this scar was infiltrated with mononuclear cells as were also the scars in the adventitia and media of the pulmonary artery.

A woman,‡ 34 years old, showed at autopsy a severe syphilis of the arterial system which involved the entire aorta as far as the origin of the superior mesenteric artery, the great vessels of the neck and both subclavians. One of these was totally obliterated.

In this group, Barth's case is the most conclusive and is also the most recent.

There remain a number of cases frequently included as possible instances of syphilis of the pulmonary artery, in which the evidence is not sufficient to include them in any of the above groups. Among these are two cited by Wagner and Quiatkowski from Virchow. Concerning one of these Virchow,[25] himself said: "Ob der sonderbare Nodulus auf der Wand der Lungenarterie ein Syphilitisches Condylom war, muss ich unentschieden lassen." Another doubtful case by Dickinson[26] is included in Posselt's Review.

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* Friedreich. Syphilis des Herzens, Wien, 1889, 67; cited by Posselt. Ergebnisse der allg. Path. und path. Anat., Lubarsch und Ostertag, 1909, 471.

† Henschen. Sammlung Klinischer Vorträge. Neue Folge innerer Medizin, 1906, Nr. 126, 595.

‡ Westenhoeffer-Verein f. inn. Med. in Berlin, 1906; cited by Posselt in Ergebnisse der allgemeinen Pathologie und path. Anatomie, Lubarsch und Ostertag, 1909, 471.

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In three others only one of the branches of the pulmonary artery was involved. Ribbert's [27] case showed a typical mesaortitis; the adventitia of the aorta contained typical gummatous masses which surrounded the occluded branch of the pulmonary artery.

In McPhedran and Mackenzie's [28] case the endarteritis of the right branch of the pulmonary artery was considered to be syphilitic on account of the presence of miliary gummata in the liver, although there was no other evidence of the disease in the body.

Payne [29] makes no mention of the larger branches of the pulmonary artery. In one lung there was periarterial thickening involving the media and intima. On account of the distribution and histological picture of the lesion he concluded that the process was probably due to syphilis, although there was no other evidence of the disease.

In his review of aneurysm of the pulmonary artery, Henschen [30] includes a number of cases in which the data in the original reports are insufficient for him to determine the nature of the associated sclerotic changes in the vessel wall, even though he feels that in the majority these may have depended upon syphilis.

The two cases of mesarteritis of the pulmonary artery, recorded below, present anatomical changes in the vessel wall similar to those in mesaortitis. In the first, the clinical history, the positive Wassermann reaction and the presence of lesions elsewhere in the body indicate that syphilis is the etiological agent. In the second there are much more extensive lesions in the pulmonary artery, even aneurysm formation, but the negative clinical history and Wassermann reaction and the absence of other more characteristic lesions of syphilis in the body makes the decision concerning the etiology of the vascular changes more difficult.

Case I.—L. C., a colored male, aged 27 years, was admitted to the surgical clinic of The Johns Hopkins Hospital in the service of Dr. W. S. Halsted, on April 29, 1913.

He had had gonorrhea several times and a chancre followed by a characteristic secondary syphilis at the age of 17 years.

On admission the patient complained of a swelling in the right groin. At first the nodule was quite small but with increase in size there was severe pain which radiated towards the right knee.

On physical examination no general glandular enlargement was noted. The retro-manubrial dulness was increased towards the left.

The patient had a brassy cough which was aggravated in the decubitus position. X-ray examination revealed a circumscribed dilatation of the aorta. The Wassermann reaction was positive.

There was an expansile, pulsating oval mass in the right groin. On May 5 a silver band was placed around the external iliac artery just above this

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aneurysm. The operation was followed by a slight decrease in the pulsation of the sac. The patient's general condition became alarming. He had difficulty in breathing. The brassy cough was exaggerated. On May 9, his temperature and pulse, which had been normal, suddenly rose to 105° F. and 165 respectively. This was associated with signs of pneumonia, to which the patient succumbed several days later. The autopsy was performed four hours after death.

Autopsy 3927. Anatomical Diagnosis. *Primary.*—Syphilitic mesarteritis of the aorta, pulmonary splenic and right femoral arteries; saccular aneurysms of the arch, descending aorta, splenic and right femoral arteries, fibrous orchitis; syphilitic cirrhosis of the liver. Healed gumma (?) of kidney.

Subsidiary.—Pseudolobar pneumonia with abscess formation and organization, fibrino-purulent pleurisy.

The *body* is that of a well-nourished colored male, 157 cm. in length. There is marked exophthalmos. The pupils are regular and equal. The entire body is covered with puckered, slightly atrophic, brownish pigmented scars, averaging 0.5 cm. in diameter. The penis is extensively scarred. *Just above the right Poupart's ligament is a recent surgical incision. Below Poupart's ligament on the same side is a soft, irregular mass about 6 cm. in its longest diameter.*

Peritoneal Cavity.—The spleen is bound down to the diaphragm by fibrous adhesions.

The *left pleural cavity* presents nothing of interest. The *right pleural cavity* contains about 200 c. c. of slightly yellow fluid.

The *pericardial cavity* contains a few cubic centimeters of clear, straw-colored fluid. Its serous surfaces are smooth and glistening.

The *heart is of normal size. The surface is smooth.* The epicardial fat is not increased. The right auricle is not enlarged. Its wall is not thickened. The endocardial surface is smooth and glistening. The foramen ovale is closed. The tricuspid ring measures 12.5 cm. The valves, chordæ tendineæ, and papillary muscles are delicate and smooth. The right ventricle is normal. The pulmonary ring measures 8 cm. Its cusps are delicate, transparent and normally attached. *The intimal surface of the common pulmonary artery, as well as that of the branches as far down as their smallest ramifications is irregularly corrugated. This is brought about more by irregular linear, or radiating translucent, greyish-white depressions than by actual thickening of the intima itself. There is a marked absence of arteriosclerotic patches, calcification and ulceration. The left auricle is normal in every respect.* The mitral ring measures 9 cm. Its valves, chordæ tendineæ, and papillary muscles are not implicated. The wall of the left ventricle averages 12 mm. in thickness. The chamber is not dilated. The aortic cusps are delicate, semi-transparent and normally attached.

The myocardium on tangential section has a uniform, reddish-brown color. *The aorta through its entire length is greatly thickened and presents an extensive "bark-like" pattern throughout. The depressions, often irregu-*

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lar with radiations from their periphery, are pale pinkish grey; between them the intima is thickened and frequently more translucent. There is a marked absence of calcificaiton and ulceration. At the origin of the innominate artery there is a saccular aneurysm, 3.4 cm. in diameter. The sac contains a small laminated clot, which covers an erosion on the outer wall of the trachea just above the bifurcation. The descending aorta presents numerous, saccular aneurysms, the smallest 1 cm., the largest 2.5 cm. in diameter.

Lungs.—The lower and middle right and a large part of both the left lobes are dark red, firm and non-air-containing, with a dry and granular pleural surface. On section they are grey and finely granular, with scattered clusters of more yellowish, opaque granules. From the latter, droplets of pus can be squeezed. The remaining portions of both lungs present a smooth glistening pleura. They are soft, air-containing and of a pink color. *At the hilum of each lung about the bronchi and pulmonary vessels is an extensive puckered scar with radiating, bluish-white, translucent lines passing out into the surrounding tissue. In the middle right lobe are several bluish-white puckered scars with radiating bluish-white bands. The hilic lymph glands are normal in size and appearance.*

The *spleen* weighs 150 gm. and measures 11 x 6.5 x 3.5 cm. In places the capsule is somewhat thickened and milky. The spleen is firm and dark red or purple. On section the capsule and trabeculæ are slightly thickened, the vessels gape; the Malpighian corpuscles are distinct but not enlarged; the pulp is not increased.

The *stomach and duodenum*, externally and when opened, appear normal. The common bile-duct and pancreatic duct are patent.

The *pancreas* is normal in appearance. The consistence is not increased and the lobulation is distinct. *At the upper border of its middle third there is a saccular dilatation of the splenic artery, about 2 cm. in diameter in which there is a laminated clot.*

The *liver* weighs 1550 gm. and measures 25 x 18 x 7 cm. *Its surface presents many puckered and linear atrophic areas, which on section extend as broad tapering, greyish-white scars deep into the liver parenchyma.* The liver is firm, pale, brownish and on section between the scars the normal architecture is readily seen.

The *adrenals appear normal.*

The *kidneys* weigh 425 gm. The left kidney measures 12 x 5.5 x 5 cm. The capsule strips readily leaving a smooth, dark purple surface. The kidney is rubbery in consistence. On section the cortex averages 8 mm.; the striations are regular, the glomeruli large and purple, the striæ of the pyramids pronounced and the pelvis normal.

The right kidney is similar to the left except that its pelvis, anterior half and the perirenal tissue has been converted into a bluish-white translucent mass whose cut surface appears granular and whose margin is scalloped.

The *pelvic organs* all appear normal.

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The *small and large intestines* including the rectum present nothing of interest.

The *testes* are small and firm. On section they are extensively scarred.

The *neck organs* appear normal.

Femoral Aneurysm.—Just below Poupart's ligament, occupying Scarpa's triangle, the right femoral artery is dilated into a saccular aneurysm, 13 x 10 x 6 cm. This has caused some erosion of the upper ramus of the pubis upon which it lies. The capsule of the hip-joint has been greatly thinned by pressure, posteriorly the aneurysm has ruptured by a very fine opening, and there is a walled-off blood clot under the medial portion of the psoas muscle.

MICROSCOPICAL NOTES.

Heart.—The fibers and their nuclei are somewhat larger than normal. There is no proliferation of the interstitial tissue.

Common Pulmonary Artery.—The intima is thickened. The media is traversed here and there by strands of scar tissue, containing blood-vessels. There is no cellular infiltration in any of the coats.

Left Pulmonary Artery—Longitudinal Section.—The intima is not involved. The elastic and muscle fibers of the media are extensively broken by strands of scar tissue containing blood-vessels and infiltrated with small round cells. These scars take either a transverse or a longitudinal direction. The adventitia is greatly thickened and composed of coarse, hyaline fibrous tissue poor in nuclei. Scattered through this are foci of small round cells, frequently clustered about a blood-vessel. Section through the scar at the hilum of the right lung including the pulmonary artery shows several nodular structures in the vessel wall which bulge into the lumen and slightly compress the media. These nodules consist of a dense mass of epithelioid and round cells at the periphery of a caseous or necrotic center. One giant cell also was found in the wall of such a nodule. The media of the vessel shows no change, but the adventitia is enormously thickened by coarse, hyaline bands of fibrous tissue, which unite it with a similar, more cellular mass of scar tissue around the bronchus. The wall of this bronchus is also infiltrated with round cells and its epithelium is absent. The neighboring alveoli show metaplasia of their lining cells wherever the cicatrix extends into the lung parenchyma.

Section of the scar at the hilum of the left lung also includes several branches of the pulmonary artery and the bronchus. Most of the vessels show round-cell infiltration of their walls. In one there has been a complete occlusion of the lumen with secondary canalization. The walls of the bronchi are also infiltrated with round cells. Surrounding these structures there is an extensive hyaline scar tissue in which numerous foci of round cells occur. Many of the smaller vessels in the scar are completely occluded by intimal proliferation.

Other sections of the lung show typical lobar pneumonia, complicated by small abscesses and early organization. Over large areas connective-tissue plugs fill alveoli.

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Spleen.—The capsule, trabeculæ and Malpighian bodies show no change. The blood sinuses are greatly overfilled; their basement membrane is thick and hyalinized; their endothelial lining cells are swollen.

Wall of Aneurysm of Splenic Artery.—The intima is converted into a hyaline mass in which only a few pale nuclei are seen. The media is broken by scars, rich in round cells. The adventitia is markedly thickened by partly hyalinized scar infiltrated with small mononuclear cells which frequently occur in dense masses. The lumen of the vessel is filled with a partly hyalinized thrombus.

The *liver* shows chronic passive congestion. *Section through one of the scars presents the usual deformity around a mass of hyaline fibrous tissue.*

The *pancreas* is negative.

The *kidneys* show chronic passive congestion. *A section through the entire anterior half of the right kidney to include the mass in its pelvis presents a large area of hyaline fibrous tissue, inseparable from a greatly thickened and similar appearing capsule, with a periphery of very cellular scar tissue, rich in round cells. Renal tubules and glomeruli occur in the scar but present various stages of atrophy and fibrosis.*

Testicle.—The tunica albuginea is greatly thickened and diffusely infiltrated with round cells. The membrana propria of the seminiferous tubules is increased in width. The intertubular connective tissue is increased and infiltrated with round cells; there is also some atrophy of the tubules.

The *prostate* is negative.

Thyroid.—The acini are distended with colloid and their epithelial lining cells are low.

Case II.—F. C., a colored male, aged 56 years, was admitted to the Medical Clinic of The Johns Hopkins Hospital in the service of Dr. L. F. Barker, on June 8, 1912.

His complaint was "shortness of breath."

He had had the usual diseases of infancy and childhood and at the age of 21 "lock-jaw" after an injury to a finger. At this time also he had an eruption on his back. There is no history of any venereal disease.

For six or seven years previously the patient had noticed that his feet were somewhat swollen at the end of the day. In the last two years he had frequently been compelled to discontinue work on account of general muscular soreness and backache. Shortness of breath had developed about a year before admission and had rapidly become worse. Then the feet and abdomen had become swollen and later cough, polyuria and nycturia had all helped to completely incapacitate him.

On admission the patient had marked orthopnœa; cyanosis of the head and neck; moderate general glandular enlargement and râles throughout both sides of the chest. The heart sounds were distant, blurred and irregular. The abdomen was distended with ascites and the legs were slightly edematous. The abdomen was repeatedly tapped but the ascites recurred. The cardiac condition did not improve and the patient died with evidences of decompensation. The Wassermann test, performed on June 5 and June 25 respectively, was negative on both occasions. The autopsy was performed 19 hours after death.

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Autopsy No. 3763.—Anatomical Diagnosis. Cirrhosis of both lungs; fibrous pleurisy; miliary gummata or tubercles of the liver; mesarteritis of the pulmonary artery; aneurysm of the right main branch with partial thrombotic occlusion of sac and vessel; dilatation and hypertrophy of the right ventricle; chronic passive congestion of the viscera; ascites; edema of the extremities.

The *body* is that of a fairly well nourished colored male, 162 cm. long. The pupils are equal and measure 4 mm. in diameter. The abdomen is distended and the external genitalia and legs are edematous.

The abdominal cavity contains a large amount of opalescent greenish-yellow fluid. The serous surfaces are everywhere smooth and glistening. On the parietal peritoneum there are a few small translucent greyish nodules several millimeters in diameter. The liver is enlarged and extends a fingerbreadth below the costal margin in the mammillary line.

The pleural cavities are partly obliterated by old fibrous adhesions. On the right there is a small amount of fluid similar to that found in the abdominal cavity. On the left, where the adhesions are not so marked, the fluid is more abundant (one liter).

The pericardial sac contains about 500 c. c. of clear yellowish fluid. The pericardial surfaces are smooth and glistening.

Heart.—The heart weighs 520 gm. Both the right auricle and ventricle are markedly enlarged. The epicardial surfaces are smooth and glistening and the fat is abundant. The wall of the right auricle is thickened, the cavity dilated; the triscupid ring measures about 15 cm.; the valves are slightly thickened at the insertion of the chordæ. *The right ventricle is greatly dilated and hypertrophied; its wall measures 8 mm. in thickness. The pulmonary valves are delicate, the pulmonary artery is considerably widened; at the orifice it measures 8.5 cm. in circumference and this increases to 10 cm. in the main stem. The wall of the pulmonary artery is thickened and inelastic and the intimal surface has an appearance similar to that in an extensive syphilitic mesaortitis. Between the contractures, which may be linear or irregularly round or oval, the intima is thickened and more translucent than normal. There is a marked absence of yellow ulcerated or calcified plaques. Two of the above contractures bulge outwardly distinctly. These are located just a short distance above the pulmonary valve. Section through such a scar shows the intima and adventitia bound together by a silvery grey or reddish band, replacing the media. On the posterior wall of the right branch of the pulmonary artery is a laminated thrombus, which narrows the lumen of the vessel considerably. A section through the center of this thrombus shows that it arises in a small saccular dilatation of the vessel wall about 2 cm. in diameter in which the coats of the vessels are no longer to be made out distinctly. The aneurysmal sac presses directly upon the trachea but has not eroded into it.* The lymph glands at the bifurcation and in contact with the pulmonary artery are enlarged and soft. One of them, somewhat more deeply pigmented than the remainder, contains a small fibrocaseous mass in its center, which stands out distinctly upon the black background as a

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chalky white area. The periarterial and peribronchial fibrous tissue in the anterior mediastinum is in general much more dense than normal. This is particularly true around the pulmonary artery and its branches. The left auricle is normal in size and general appearance as is also the mitral valve and the left ventricle. The mitral ring measures 10½ cm. The aortic valves are delicate as is also the base of the aorta and coronary artery. The wall of the left ventricle measures only 1 cm. in thickness.

Lungs.—The right lung is removed with a great deal of difficulty on account of the dense adhesions between the two pleural layers. The lung is small. The hilic structures do not present any marked abnormalities. The pulmonary arteries show some slight changes characterized by alternating yellowish and more translucent, greyish areas. On section numerous linear or irregular black scars may be seen throughout the lung tissue. Between such scars the lung tissue is pale brownish pink and air-containing. The bronchi are drawn together. The bronchioles everywhere are slightly dilated and their mucous membrane is congested.

The pleural adhesions are not so extensive on the left and the lung is much more voluminous; otherwise it resembles the right in almost every respect. At the hilus the pulmonary artery is greatly dilated and shows an irregularly thickened and scarred surface similar to that described in the larger branches of the vessel. Many of the branches of the pulmonary artery within the lung contain small thrombi, which are still friable and only occasionally adherent to the vessel wall.

The *spleen* weighs 250 gm. and measures 13 x 7.5 x 4.5 cm. Its capsule is irregularly thickened, yellowish or bluish gray in appearance. It retains its shape after removal and has a rubber-like consistence. On section the fibrous trabeculæ are quite prominent, as are also the blood-vessels. There is very little excess of splenic pulp and the Malpighian bodies are inconspicuous.

Stomach.—The mucosa is everywhere edematous and congested; it shows a few small polypoid thickenings. The duodenal mucosa has a similar appearance, but is covered with a bile-stained mucus.

The bile and pancreatic ducts empty together about 8 cm. from the pylorus of the stomach and are patent throughout.

The *pancreas* is normal in size and appearance.

The *liver* weighs 1750 gm. and measures 24 x 17 x 6 cm. It has a purplish color, which, however, becomes reddish brown as soon as the organ is removed and sectioned. On section the lobules seem enlarged; the periportal tissue stands out prominently on account of its yellowish color, while the tissue about the central veins is often of a deep black color and markedly depressed.

The *adrenals* are normal macroscopically.

The *kidneys* weigh 375 gm. The left kidney measures 13 x 5.5 x 4.5 cm. The capsule strips readily leaving a smooth pale, purplish-brown surface on which a few small cysts may be made out. On section the cortex of the kidney measures about 6 mm. in thickness; the striations are very distinct, the blood-vessels are everywhere congested and the glomeruli are much

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enlarged and stand out as translucent cherry-red dots. The pyramids are very much more congested than the cortex; the pelvis is normal.

The right kidney resembles the left in every respect.

Pelvic Organs.—The urinary bladder is small. Its mucosa is slightly edematous but pale pinkish in color. The urethra, prostate and testes show nothing abnormal macroscopically.

Neck Organs.—At the base of the tongue the papillæ are slightly less prominent than normal and near the epiglottis the tongue has a quite smooth surface. The esophagus is pale and shows nothing abnormal. The larynx and pharynx appear normal.

The *aorta* is quite elastic throughout. Aside from a very few small yellowish atheromatous elevations it appears normal.

Intestines.—The mucosa is congested; otherwise the intestines show nothing abnormal.

Microscopical Notes.—Sections of the pulmonary artery show a picture which is exactly similar to that described for syphilitic aortitis. There is a dense inflammation of the adventitia characterized by the new formation of vascular fibrous tissue very rich in mononuclear cells. This inflammatory process of the adventitia extends into and replaces the media. The intima overlying such areas may be greatly thickened and hyaline. In the adventitia particularly, but also in the media, occasional zones of hyaline necrosis surrounded by epithelioid and round cells occur. These resemble large fibrous tubercles. The inflammatory mass binds the pulmonary artery quite closely to the trachea and other structures with which it comes in contact.

The lungs are densely scarred so that in some areas the alveoli are entirely replaced by hyaline fibrous tissue often infiltrated with round cells. In such zones the bronchi are dilated; the blood-vessels are engorged and their walls thickened, but in none of the sections do the vessels show a specific process similar to that described in the main stem of the pulmonary artery.

The pleural surface is very much thickened and composed of a dense mass of hyaline fibrous tissue.

Examination of many sections of the lung shows here and there a concentric mass of hyaline tissue more or less densely infiltrated with pigment.

Liver.—One miliary nodule composed of a central giant cell and surrounding epithelioid and round cells is found.

The other organs only show chronic passive congestion.

The fibrocaseous peribronchial lymph glands show no tubercle bacilli.

Discussion.—In both of these cases, although many sections were examined, silver impregnation for the spirocheta pallida was negative. In the second case, many suggestive coiled strands were found, but these were always associated with similar coarser ones that were undoubtedly elastic fibers. In no instance did the section include a

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caseous nodule, where the likelihood of demonstrating the organism is maximal.

On the other hand, sections of the pulmonary artery in both cases showed typical mesarteritis which, in the second especially, was very pronounced. In both, besides the round-cell infiltration about the vasa vasorum and throughout the thickened adventitia, besides the interruption of the media by hyaline or cellular granulation tissue, besides the thickened hyaline intima, there were small, caseous nodules, surrounded by epithelioid and round cells in the wall of the vessel.

Such a lesion in the aorta is at present considered to be pathognomonic of syphilis.

In the first case, the assumption that the process was brought about by the virus of syphilis is strengthened by the very extensive similar involvement of the aorta. Here the lesion affected not only the thoracic oarta, but extended through its abdominal portion, where it was associated with numerous small aneurysms, into the iliac and femoral arteries. In the latter vessel an aneurysm had also resulted. A similar change in the wall of the splenic artery with aneurysm was found.

It is interesting that the extensive involvement of the aorta and pulmonary artery was not associated with any symptoms and that the patient entered the hospital to seek relief from the femoral aneurysm.

It is needless to say that such extensive vascular disease is very rare. In one instance of pulmonary mesarteritis recorded by Westenhoffer, there was a similar change of the aorta as far as the origin of the superior mesenteric, the great vessels of the neck and both subclavians, one of which was totally occluded.

In the first case, the etiology of the lesion of the pulmonary artery is practically established by the positive history, the scars of the liver, the fibrous orchitis and the positive Wassermann reaction.

In the second case, the history, negative for syphilis, the Wassermann twice negative, all make the determination of the etiology of the lesion of the pulmonary artery more difficult.

The anatomical characteristics of mesarteritis may not be sufficient to preclude other etiological agents besides the spirocheta pallida. It is natural, therefore, that the presence of a fibro-caseous nodule in a bronchial lymph gland and a fibrous pleurisy suggested the possibility that these, as well as the changes in the pulmonary artery and the atypical cirrhosis of the lung might be tuberculous. A search for tubercle bacilli throughout all of the tissues was vain.

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The changes in the lung were those that are considered to be brought about most probably by the virus of syphilis.* A similar involvement of the lung occurred in the first case, as well as in a large proportion of the cases above cited from the literature (Hanford, Wagner and Quiatkowski, Brooks, Barth, etc.). This peculiar pulmonary fibrosis, which is most marked at the hilus, and extends through the lungs as fingerlike projections along the course of the larger vessels and bronchi, is rare. Its frequent association with another rare lesion, pulmonary mesarteritis, also supposed to be caused by syphilis, strengthens the presumptive evidence in favor of this etiology.

Furthermore, the papillæ at the base of the tongue in this case were partly obliterated and its surface was more smooth than normal, another lesion often interpreted as the result of syphilis. Finally, there was a miliary tubercle or gumma in the liver.

In the second case, the right branch of the pulmonary artery was the seat of a small aneurysm, very similar to the one in Barth's case cited above. It would lead too far to discuss aneurysm of the pulmonary artery here. Henschen has recently collected a large number of cases, and in his review of the subject he concludes that the two most important etiological factors in the production of aneurysm of the pulmonary artery are anomalies, such as patent ductus arteriosus, which increases the tension in the stem of the pulmonary artery, and syphilis. Henschen himself admits that there is not a sufficient anatomical basis to conclude that syphilis is the cause of the associated change in the vessel wall in the majority of instances.

In his own case, however, the aneurysm was undoubtedly superimposed upon a mesarteritis.

Conclusions.

Mesarteritis, so frequent in the thoracic aorta, occurs rarely in the pulmonary artery and other large vessels.

Although the evidence is not so conclusive here as in the aorta, the lesion is most probably caused by the virus of syphilis.

Gummata are not infrequent accompaniments of the medial and adventitial scars in the pulmonary artery and may occur without the latter.

*** It must be borne in mind that so far no conclusive anatomical evidence of the specific nature of pulmonary syphilis in the adult has been forthcoming.**

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Aneurysm formation often complicates the mesarteritis in any of these larger vessels.

The lesions in the pulmonary artery may occur alone, or be only part of a widespread vascular disease.

A fibrosis of the lung, most marked at the hilus, in itself a rare lesion, occurs in a large percentage of the cases of pulmonary mesarteritis.

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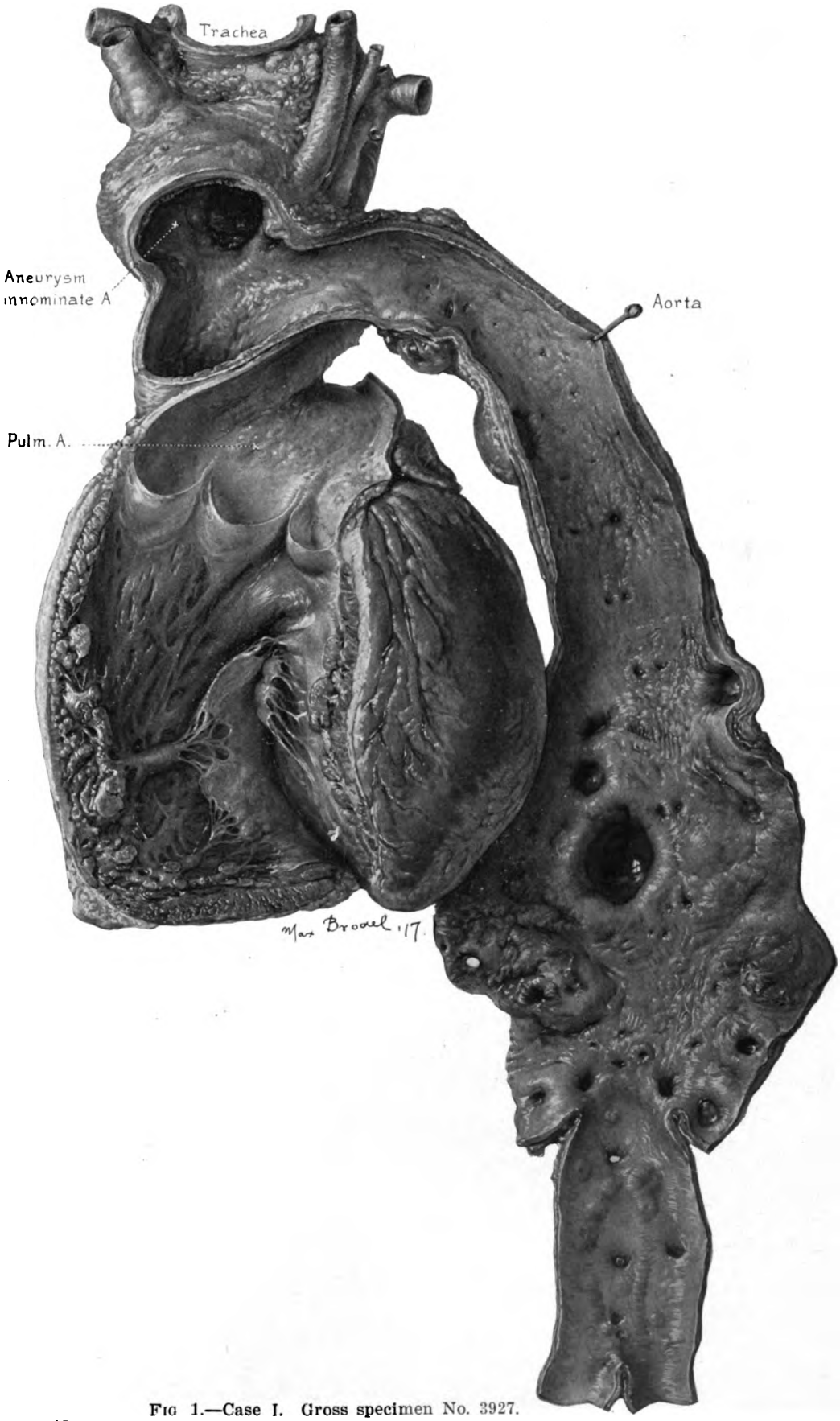

FIG 1.—Case I. Gross specimen No. 3927.

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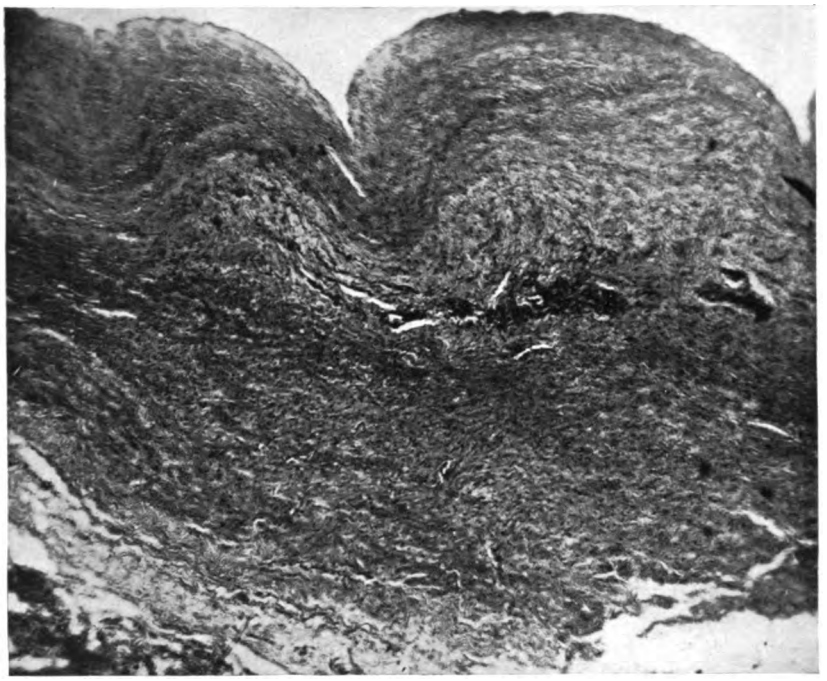

FIG. 2.—Case I. Pulmonary artery. H. & E. stain. (× 50.) Shows scar tissue in the media, retraction of the intima and perivascular small-round-cell infiltration of the adventitia.

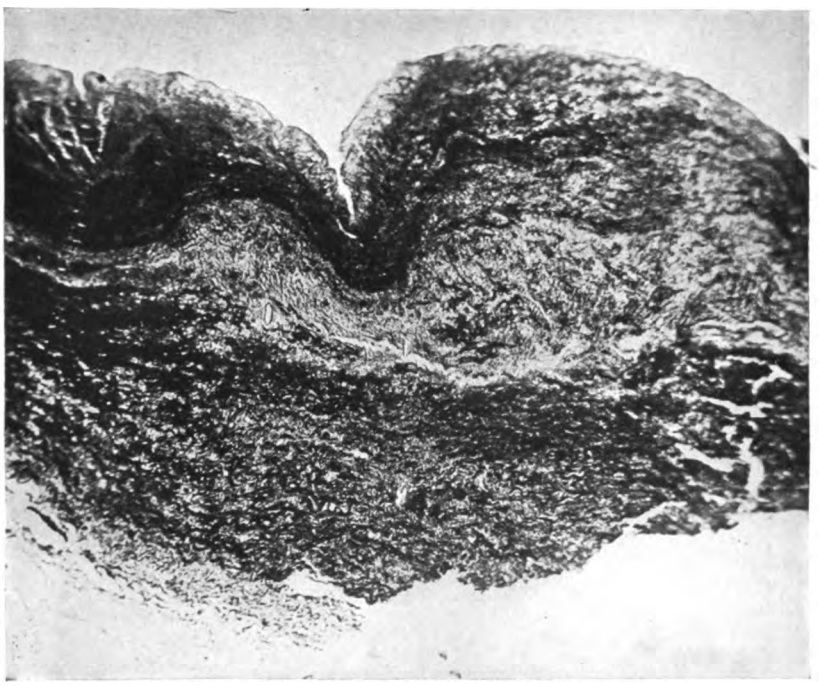

FIG. 3.—Same field as Figure 2. Elastic stain + carmine. (× 50.) Shows degeneration of the elastic fibers of the media in the region of the scar tissue.

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FIG. 4.—Media of Figure 2. A higher power. (× 224.)

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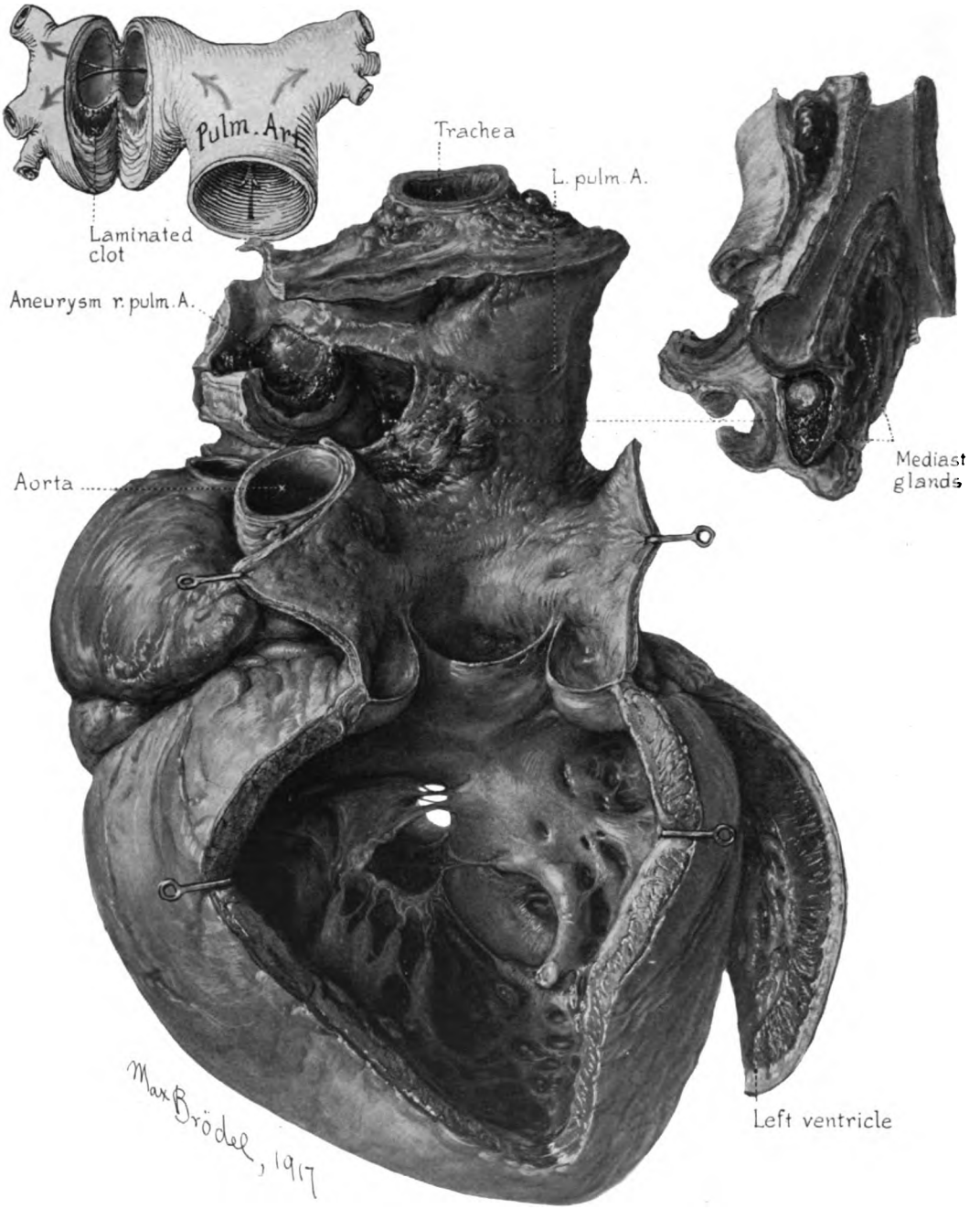

FIG. 5.—Case II. Gross specimen. No. 3763.

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FIG. 6.—Case II. Pulmonary artery. H. & E. stain. (× 25.) Shows scar tissue and focal necrosis in the media, retraction of the intima and small-round-cell infiltration about the vessels of the adventitia.

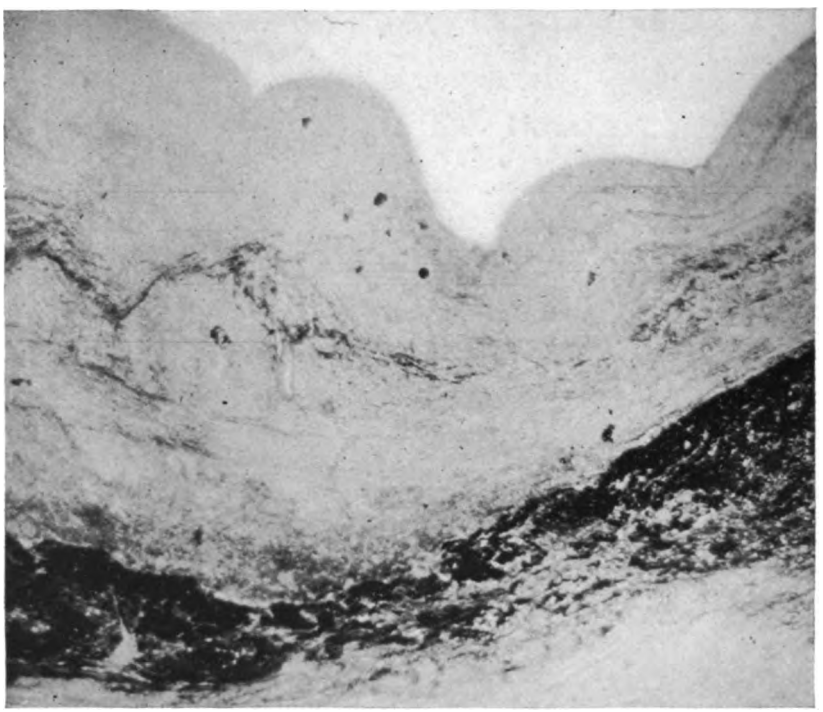

FIG. 7.—Same field as Figure 6. Elastic stain + carmine. (× 25.) Shows broken elastic fibers in the scarred area of the media.

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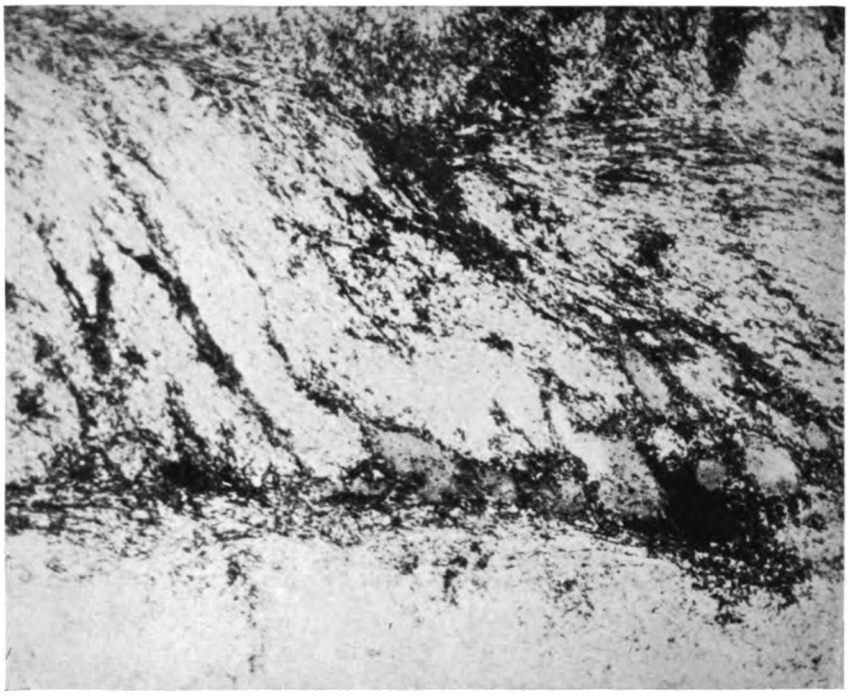

FIG. 8.—Media of Figure 6. Higher power. (× 77.)

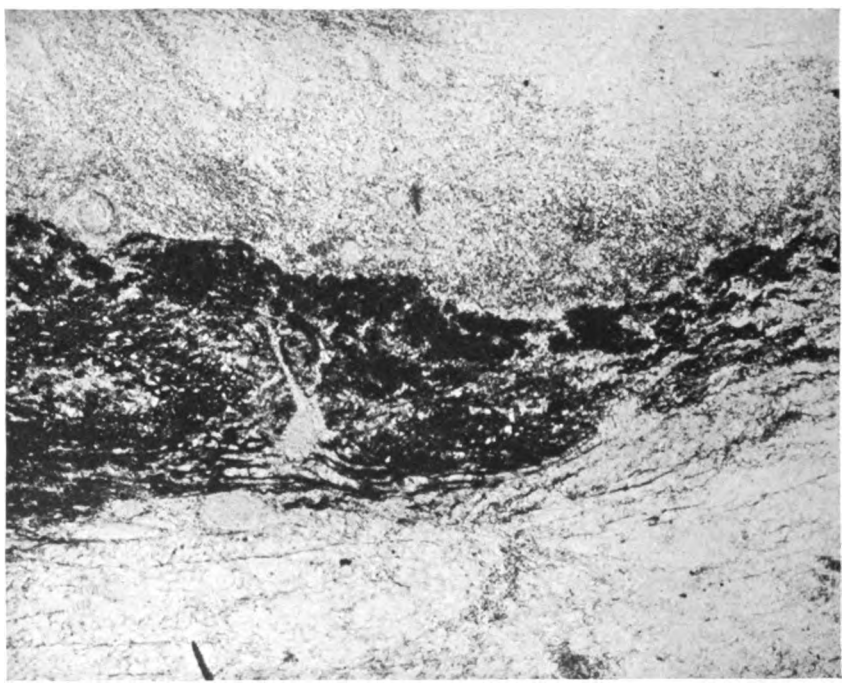

FIG. 9.—Media of Figure 7. Higher power. (× 66.)

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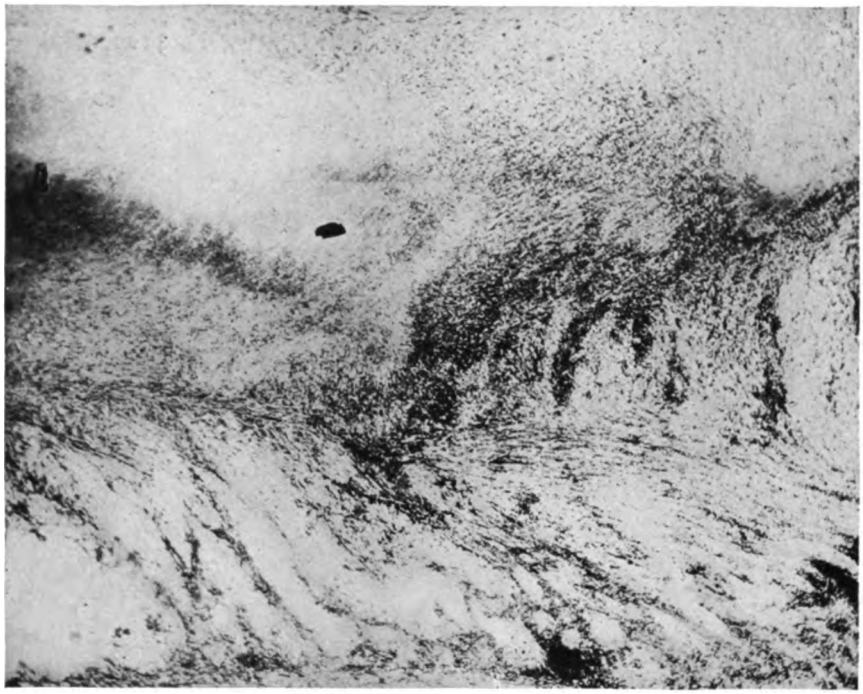

FIG. 10.—Media adjacent to field shown in Figure 6. A higher power. (× 45.) Shows scar tissue below and two foci of necrosis with nuclear fragmentation and a zone of epithelioid and small round cells above.

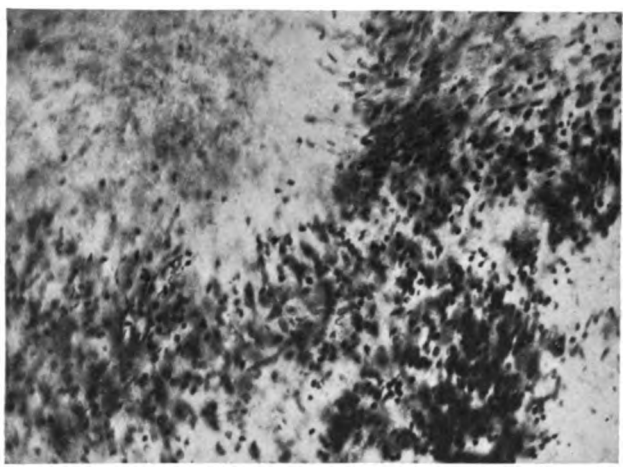

FIG. 11.—One of the foci of necrosis of Figure 10. A higher power. (× 158.)

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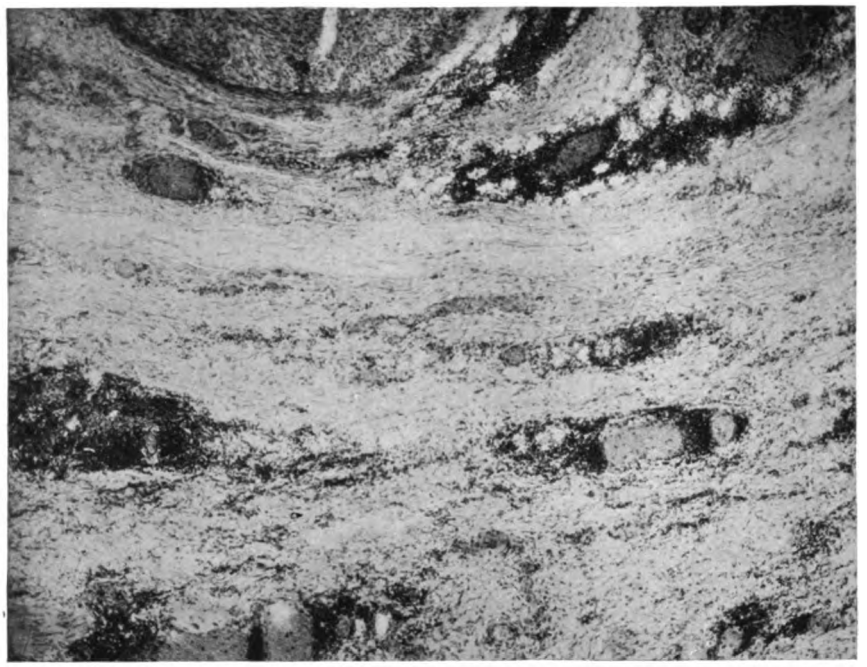

FIG. 12.—Adventitia adjacent to field shown in Figure 6. (× 58.) Shows perivascular small-round-cell infiltration.

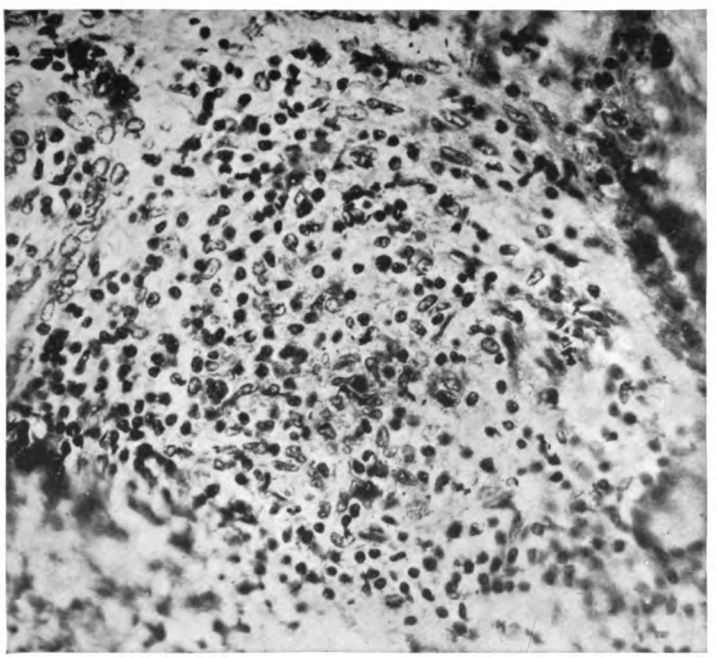

FIG. 13.—Case II. Miliary nodule of liver. H. & E. stain. (× 306.) Shows epithelioid cells and small round cells with early central degeneration.

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A CLINICAL AND PATHOLOGICAL STUDY OF TWO CASES OF MILIARY TUBERCLES OF THE CHOROID.*

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Jaeger,[1] in 1855, first described ophthalmoscopically a choroidal tubercle † and his observations were confirmed by von Graefe and Leber.[2] The earlier ophthalmologists, however, insisted that ophthalmoscopic changes in tuberculous meningitis were rare, and it is with no little interest and surprise that one reads the comparatively recent observations of Carpenter and Stephenson,[3] who claimed to have found choroidal tubercles in 50 per cent of their cases. Following close upon their communication, we find the work of Marple[4] in the Babies' Hospital, N. Y., who concludes that in tuberculous meningitis choroidal miliary tubercles are the rule (100 per cent in 13 cases), a statement made at the Ophthalmological Congress in Oxford in 1912. And yet, in contradiction to Marple, we find Heinzel[5] with negative findings in 41 cases of tuberculous meningitis which he examined. We have, then, in these latter days, in opposition to the rather conservative statements of the earlier ophthalmologists, the figures of Carpenter and Stephenson, and of Marple, who place the percentage at from 50 per cent to 100 per cent. These more recent figures are based upon frequent examinations, a fact that indicates how often the changes were overlooked in olden times, when one routine examination was made and often nothing was found. The eye-grounds were not subjected to further examination, and the case was recorded as negative, so far as tubercles in the choroid were concerned. It should be remembered that the tubercles are usually seen among the terminal events in the history of the case, and ophthalmoscopic examinations should be made frequently. Marple mentions a case in which an ophthalmoscopic examination made at 6 p. m. disclosed fundi entirely free of tubercles, but at 10 p. m. a tubercle was found, this having developed

* Read before the American Ophthalmological Society, Congress of American Physicians and Surgeons, Washington, May 10, 1916.

† Whether it was miliary or not has since been questioned.

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in the interval. The introduction of the electric ophthalmoscope makes examinations of this character much easier. Not only is the fundus seen perfectly, but the great difficulty in conducting successfully an examination of this character in the case of a baby is reduced to almost a minimum, since we possess a brilliant, steady, and uniform illumination. It is certainly easy to overlook changes of this nature when using an ordinary non-electric ophthalmoscope, an examination with which often presents great difficulties.

In the first case, the tubercles, three in number, were found in the right eye above the disc, and at an angle of 120 degrees from the vertical meridian; in the left eye there was a tubercle above, one below, and one to the nasal side of the disc. In the second case there was a tubercle in the right eye above the disc and one far out to the temporal side. What was seen in the left eye could not be regarded positively as a tubercle. It might be well to state here that it is important to make an examination of both eyes, for the tubercles often occur in one eye and not in the other. It is not necessary to describe them ophthalmoscopically, as their appearance is sufficiently familiar to us all.

What is particularly striking in connection with this subject is, first, the necessity of using the electric ophthalmoscope, and, second, the importance of frequent examinations, at least twice daily. A cycloplegic should always be used. These conclusions may be equally well applied to the examinations of the eye-grounds in cases of Bright's disease. Statistics based upon infrequent examinations may be regarded as more or less unreliable, and as giving an inaccurate idea of the frequency of ophthalmoscopic changes in nephritis. The same rule might be adopted not only in Bright's disease, but in the various blood diseases, as, for instance, pernicious anemia. In both of these diseases we are in the habit of making a routine ophthalmoscopic examination when the patients are first seen. We are less apt to repeat the examination unless subjective symptoms, such as dimness of sight, should develop and call our attention to the possibility of ophthalmoscopic changes having suddenly appeared since the first examination.

Case I.—D. Z., aged two years. The father died of tuberculosis, with hemorrhage, when the patient was sixteen months old. The mother is living and in excellent health. She has never had any miscarriages. The child at birth weighed nine pounds and was fed at the breast until she was 18 months old, when she began to eat at the table with the rest of the

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family. She has never been sick in bed, but has had pertussis. She became sleepy and cross, and not long afterward began to vomit, and did this whenever she was moved. She had no appetite and was constipated. The temperature was 99.4° F., the pulse 100, and the respirations 24. She lay in bed and rarely moved unless disturbed, with lids half shut and mouth wide open, breathing slowly, with periods of apnœa. She shunned the light and was very irritable. There was no general glandular enlargement. The neck was somewhat rigid. A few days later the spinal fluid showed a film on standing, and the eye-grounds began to show blurring of the edge of the disc; four days later tubercles were discovered in the eye-grounds.

Case II.—D. C., aged four months. The child was born at full term and had been free of illness until the present one. The onset was characterized by fever and cough. She cried a great deal and slept very little. The temperature was 102° F., and the respirations 84. She lay on the table with a distant expression, the hands tightly clenched, and the legs flexed. The reflexes were slightly exaggerated, and there were numerous tuberculides all over the body. The tubercles were found in the choroid at the first examination.

Pathological Examination.

Autopsy of these two cases revealed the following:

Case I.—General miliary tuberculosis with acute tuberculous meningitis. The portal of entry of the organism was most probably through the alimentary canal, where ulcers were found. The tubercles were widely scattered through the body, being present in the mesenteric and pulmonary lymph glands, lungs, pleura, endocardium, spleen and its capsule, liver and its capsule, and last, and most important, in the choroid membrane of both eyes.

On opening the right eye (Fig. 1) there was nothing abnormal noticed until the retina was removed, then one could see a number of just visible, slightly larger than pin-points, bluish-white, translucent nodules projecting from the black surface of the choroid. Taking the macula lutea as the posterior pole, two of these miliary tubercles were located in the upper temporal quadrant, and a third in the upper nasal quadrant. Several more were seen with a magnifying glass, but their exact position was not noted.

In the left eye, again after the removal of the retina, there were seen in the upper nasal quadrant two, and in the lower temporal quadrant one miliary tubercle rising from the choroid. They were very similar in size, shape, and appearance to those of the right eye.

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Of the left eye, a careful microscopic examination was made (Figs. 3 and 4). A section taken perpendicular to the surface, through the choroid and sclera, to include one of the small bluish-white nodules, presented the following picture: To one side of the section was seen the thick sclera, composed of rather coarse strands of wavy fibrous

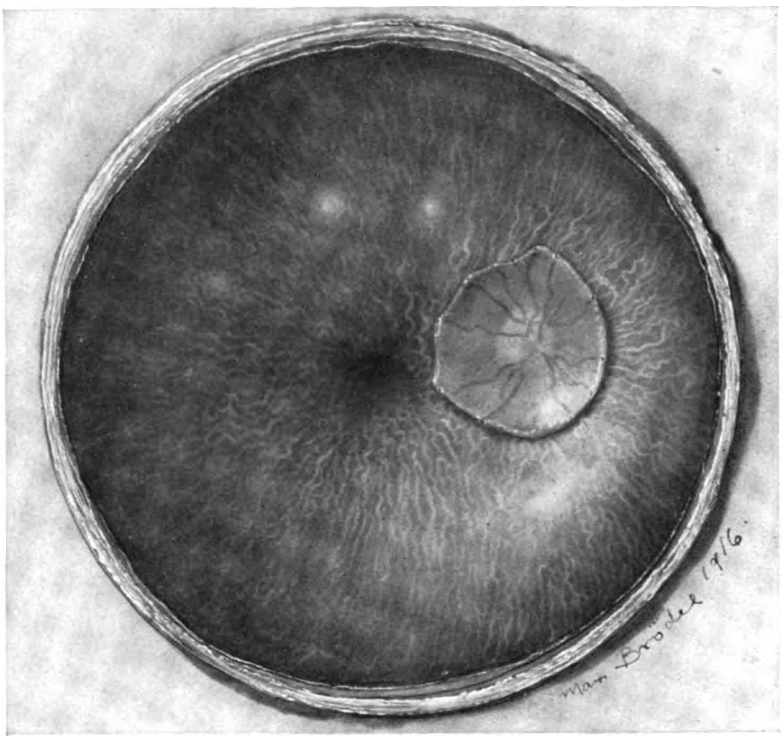

FIG. 1.—Right eye-ground of Case I. (× 5.) The retina has been removed except for a small piece still attached to the optic disc. The macula lutea corresponds to the dark central area and was taken as the posterior pole. In the upper temporal quadrant, projecting from the choroid, are two miliary tubercles. In the upper nasal quadrant, there is a third.

tissue with scattered, deeply staining, spindle-shaped nuclei. Only one or two blood-vessels were present. Joining the sclera was the choroid, a membrane of only about one-tenth the thickness of the former, and composed of loose cellular connective tissue with large pale nuclei and many blood-vessels. The fine brown pigment granules

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were found principally in the cells along the inner margin and in a single row of cuboidal cells—the retained layer of pigment cells of the retina. Limited to the choroid was a single miliary tubercle, showing the characteristic structure and constituent elements. In its center was a typical giant cell, surrounded by epithelioid cells with a peripheral zone of lymphoid cells. There was no caseation.

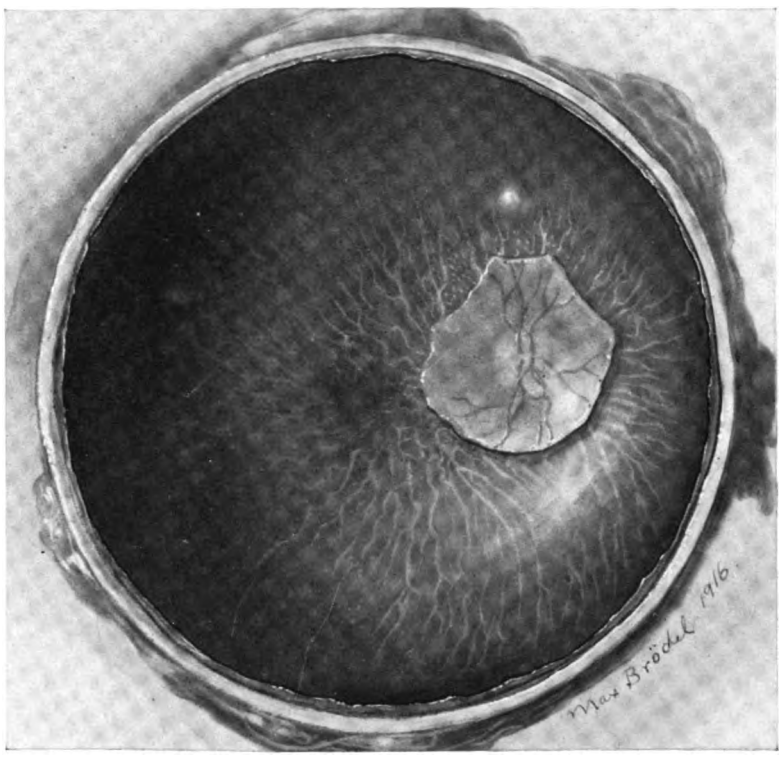

Fig. 2.—Right eye-ground of Case II. (× 5.) A small piece of the retina was left attached to the optic disc. The central dark spot locates the macula lutea, which was used as the posterior pole. In the upper nasal quadrant is seen a miliary tubercle. A second smaller one is located in the periphery of the upper temporal quadrant.

Stained sections showed tubercle bacilli in moderate number within the tubercle.

Case II.—General miliary tuberculosis without meningitis. The portal of entry was not definitely determined, but was thought to be

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through the lungs. The tubercles were found widely disseminated through the body, even involving the skin. They were present in the choroid of the right eye, but could not be demonstrated in the left.

The retina of the right eye (Fig. 2) did not appear to be implicated, and no tubercles could be seen in it; but after removal of the retina

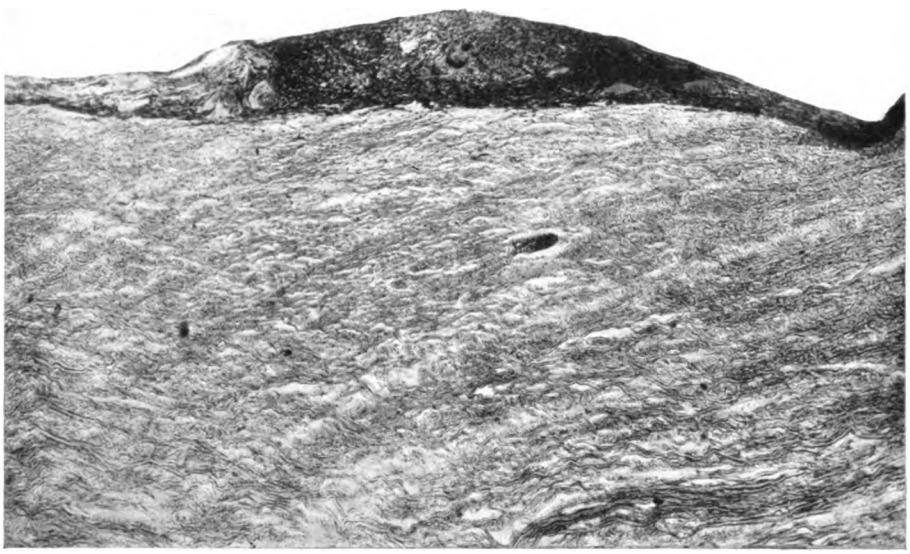

FIG. 3.—**Miliary tubercle of left eye of Case I. (× 45.) Below is the sclera and above the vascular and pigmented choroid. The tubercle is limited to the latter. It shows a typical giant cell, epithelioid and small round cells, with the characteristic grouping.**

two small, grey nodules were found in the choroid. In shape and appearance they were similar to those of the first case, except that they stood out in stronger relief from the somewhat darker choroid of the negro infant, but in size the one was almost 1 mm. in diameter, the other one just visible. The first was located in the upper nasal quadrant, slightly above the optic disc; the second in the periphery of the upper temporal quadrant.

The literature of miliary tubercles of the choroid shows that the

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first case described both macroscopically and microscopically was by Manz[6] in 1858.* Five years later, the same writer[7] added two more cases. His findings were soon confirmed by Busch,[8] who contributed the fourth case. The following year Cohnheim[9] published seven cases that he had observed during the previous winter, thus taking this

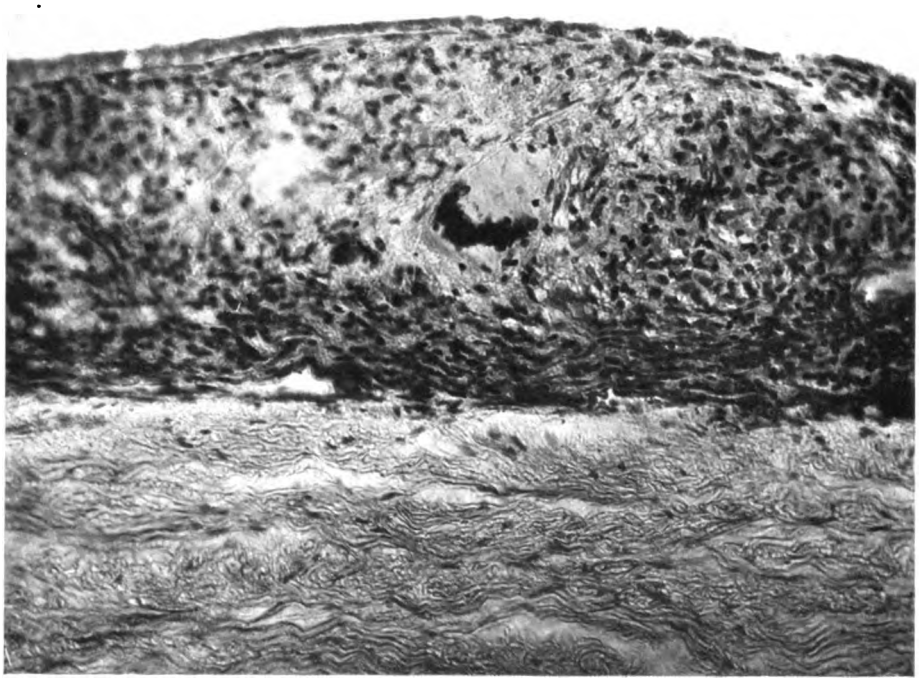

FIG. 4.—Same as Figure 3, a higher power. (× 152.) The different elements of the tubercle can be more easily recognized.

lesion out of the realm of pathological curiosities. Nevertheless, it can hardly be said that the literature is overrun with pathologic data on this subject. Isolated cases were reported, until Litten,[10] in 1877, tells us that he found choroidal tubercles post mortem in 39 out of 52 cases of acute miliary tuberculosis. Since then, the purely pathological literature has not been so abundant as might be expected.

* Jaeger in 1855 examined the choroidal nodules in his case anatomically and pronounced them tubercles, but it has since been doubted whether they were miliary tubercles.

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Most of the cases of miliary tubercles of the choroid have occurred in cases of general miliary tuberculosis with or without tuberculous meningitis. Nevertheless, it is well known that they may be found, but not so frequently, in practically any type of tuberculosis with a primary lesion almost anywhere in the body.

Conclusion.

The two cases of miliary tubercles of the choroid reported above are of interest because:

1. In the one case, we are dealing with general miliary tuberculosis with acute tuberculous meningitis; in the other, with general miliary tuberculosis without meningitis.

2. The miliary choroidal tubercles were demonstrated during life and verified at autopsy both grossly and microscopically. The tubercle bacillus was demonstrated in the lesion.

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THE BLOOD-VESSELS OF THE HEART VALVES.

By STANHOPE BAYNE-JONES, M. D.

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The interest of pathologists in the study of the process of bacterial disease of the heart valves has stimulated many contributions to the knowledge of anatomy of these structures. It is important for the pathologist to know whether bacteria become localized in the heart valves by mechanical adherence to their surfaces or by lodgment within the tissue of the valve. The latter view, which served as the basis for Köster's [1] theory of "Embolic Endocarditis," is founded upon the supposition that there are blood-vessels within the valves. Anatomical studies to determine whether or not blood-vessels are present in normal heart valves have led to such various findings that the subject has been a matter of prolonged controversy. During the past, however, there has been gathered enough positive evidence of vascularity of the valves of the heart to outweigh the negative results of investigators who have failed to find these vessels. The studies to be reported in this paper confirm the work of those who have described the blood supply of the heart valves, and in addition provide histological details of the vascular arrangement not hitherto noted.

Historical.

The following critical review of the important writings on the subject of the vascularity of the heart valves indicates the development of the controversy:

Luschka [2] was the first pathological anatomist to state that blood-vessels occur in the heart valves. In 1852 he published an article illustrated with pictures of valves after injection of the blood-vessels of normal hearts. Luschka found a network of vessels in the broad part of the valve with small vessels running to the line of closure, and a few vessels in the lower portions of the chordæ tendineæ. In the 1863 edition of his "Anatomie," [3] Luschka states that blood-vessels are present in the semilunar as well as in the auriculo-ventricular valves of the

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heart, and he illustrates this chapter with drawings from injected specimens of normal valves. He describes both arteries and veins in the valves, and suggests that endocarditis may be related to the presence of these vessels. He noted that it was easiest to find vessels in the aortic leaflet of the mitral valve, and correlated this finding with the great frequency of endocarditic lesions on this part of the valve. Luschka's drawings, however, do not show the details of the relationship between the various vessels, and they are incorrect in that they indicate that the capillaries end blindly in the valves. As will be shown later, there are definite vascular anastomoses here and a characteristic capillary bed. It is probable that Luschka's injection mass did not penetrate sufficiently far.

After Luschka's clear presentation of the subject, Joseph[4] immediately disputed the idea that blood-vessels are present in the valves. Since then the controversy has continued. The difficulty in demonstrating the presence of these vessels seems to have been the chief grounds for the criticism of Luschka's findings. It is obvious that Joseph did not inject the valves as Luschka did. By some prescience, the source of which cannot be deduced from the writings of Luschka, many authors decided that the valves studied by him were abnormal.

Among the influential opponents of Luschka were Coen[5] and Langer.[6] These authors found that the atrioventricular valves were partially vascularized, while normal semilunar valves never contained blood-vessels. Langer associated the presence of vessels in the atrioventricular valves with the occurrence of fibers of smooth muscle. By making this correlation, he announced a doctrine which has been invoked frequently since. Practically all subsequent studies have shown that the blood-vessels are fairly abundant wherever there are muscle fibers in the valves. These are supposed to be confined to the basal third of the valve, and it is probably the rule that in the adult these structures are limited to this region. Numerous studies of the musculature of the valve have been made. In Tandler's[7] recent "Anatomie des Herzens," the situation is summed up as follows:

> **Corresponding to their developmental process, the atrioventricular valves of the embryo contain a considerable amount of muscle and a corresponding number of blood-vessels. This musculature bears a close relationship to the auricular musculature, so that in fetal hearts and those of young children vessels are seen extending as far as this musculature. In the fetal heart and in the young heart, vessels extend from the papillary muscles to the chordæ tendineæ and along through to the valve. The**

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vessels diminish along with the muscle fibers of the chordæ and valves. The semilunar valves, which are almost devoid of muscle, are also practically devoid of vessels. When islands of muscle tissue remain in the thin portions of valves, delicate blood vessels can be shown to be present here.

In 1903, Königer[9] published an elaborate monograph on endocarditis. His studies of the normal anatomy are mostly literary, as he admits, on page 23, that he has not attempted to inject normal heart valves. He grants the vascularity of fetal valves and acknowledges that hematomata and hemangiomata are found at times in the normal valves of the new-born and young. He attributes these conditions to vascular rests in the valves, and accepts Langer's position on the absence of blood-vessels in adult valves.

The more recent studies of Nussbaum[9] are more convincing. He succeeded in finding blood-vessels in the atrioventricular valves of newborn, child and adult. His Figure II on page 465 is a sketch of the vascular network in the membranous portion of a mitral valve. He was not able, however, to inject vessels in the semilunar valves or chordæ tendineæ.

The experimental endocarditis produced by Rosenow[10] by intravenous injections of bacteria gives a pathological corroboration to the findings of the anatomists who have demonstrated heart-valve vessels. After the injection of streptococci, pneumococci and Staphylococcus albus into rabbits, Rosenow found subendothelial clumps of bacteria in the heart valves, with hemorrhages within the structure of the valve. Rosenow thinks that the localization of bacteria in the valve must depend upon the presence of small blood-vessels there, which become embolized by clumps of bacteria.

The most recent summary of the controversy has been placed by MacCallum[11] in his "Text-Book of Pathology." His own studies of the subject make him take position with Langer—limiting the vessels to the basal third of the atrioventricular valves. MacCallum states: "A very complete injection of the dog's heart can be made by clamping the aorta and injecting India ink into the carotid before the heart stops beating." My experience has been that the heart of the dog is not good material to use for such a study, and that an injection mass pushed by the pressure of a failing heart-beat has entirely too slight a force to penetrate the vessels of the heart valves. Proper pressure, a suitable injection mass and the study of cleared specimens are the factors to which I attribute the findings to be recorded here.

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Experimental Studies.

The method of demonstrating the blood-vessels in the heart valves was based upon the injection of a solution of carmin gelatin into the coronary arteries. In some cases, as Dr. M. C. Winternitz has pointed out, vessels are visible in the valves of hearts opened at autopsy. It is a relatively simple matter to insert a capillary glass pipette into these vessels and to inject their fine ramifications with India ink. In this way, however, lymphatics are not distinguishable from blood-vessels. Injections through the coronary arteries, on the other hand, give unequivocal evidence of the type of vessel thus filled with the colored mass.

The *carmin gelatin* used in these injections was prepared as follows:

Gelatin.—A 15 per cent solution of gelatin ("Gold Label") was made by slowly dissolving the requisite amount of gelatin in distilled water over a steam bath. When this was thoroughly dissolved, it was filtered several times through double thicknesses of cheese-cloth.

Carmin (Grübler's preferred).—Sufficient carmin to make a 1.5 per cent solution, when added to the gelatin solution, was pulverized in a mortar, enough water being then added to make a thick paste. The carmin was then dissolved in ammonium hydroxide of known strength. The ammoniacal solution of carmin was then quickly poured into the warm solution of gelatin and thoroughly stirred. To this mixture was added slightly less than the calculated amount of acetic acid required to neutralize the ammonium hydroxide. The color of the carmin gelatin should be dark red, almost like the color of venous blood. A light red color indicates that too much acid is present, and the carmin will be found in small granules when a drop of the fluid is examined under the microscope. If the mass is slightly alkaline, the dye will diffuse through the injected tissues. The final adjustment of the reaction of the mixture was made from data obtained by titrating small amounts of it against the solutions of ammonium hydroxide and acetic acid. The sweetish odor of the mixture when it is neutral, supplanting the acid or ammoniacal odor of the first stages of the preparation, was found to be as valuable as any other indicator of the optimal reaction of the mixture. When neutral, the mixture was filtered through double thicknesses of cheese-cloth. After the addition of a few crystals of thymol, the carmin gelatin was stored in flasks until needed. To prepare this for use, it was melted on a water-bath, and kept at 45 degrees C. during the injection.

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The preliminary experiments were performed upon the hearts of pigs, one or two years old, obtained from the slaughter house. The heart valves and chordæ tendineæ of these animals have vessels which, in microscopic sections, are seen to contain blood cells. With this assurance that the heart valves of the pig contain blood-vessels, experiments were begun with the preconceived notion that it would be a simple matter to inject the vessels with carmin gelatin. Many attempts were made before the proper conditions were found, and 46 hearts were used before a satisfactory injection was obtained. The important considerations were the post-mortem rigor of the myocardium, the presence of clots of blood or bubbles of air in the small branches of the coronary arteries, the blocking of the large blood channels so that the injected fluid would pass into the valves, and the pressure required to force the gelatin into the small lateral vessels of the annular arteries. When these factors were properly arranged for, the blood-vessels of the heart valves of the pig could be injected with regularity.

After these experiments, the procedure was as follows: The heart was used immediately, if obtained within an hour of the death of the animal. If not, it was kept in isotonic salt solution at room temperature for 24 hours, until the rigor of the muscle became soft and the vessels relaxed. The chambers of the heart were washed as free from clot as possible, by allowing water to flow through the auricles. The coronary sinus was plugged with cotton and tied off gently. The cut edges of the auricles were then closed with a purse-string suture, and the pulmonary artery was tied off as high above the valves as possible. Small glass cannulæ were then passed down the stump of the aorta into the orifices of the right and left coronary arteries and tied in place by a silk suture passed with a fine needle around these arteries near the aorta. Care was exercised then to close all open vessels and to cause no new "leaks" from tissue torn by the sutures. It was found to be of great importance to block these wider channels, so that the injection mass could be forced into the narrower course of the heart valves. By an arrangement with an air-pressure apparatus connected with a manometer, the melted carmin gelatin at a constant temperature of 45 degrees C. was pushed into the coronary vessels under a pressure of 140 to 190 mm. Hg., while the heart was kept in a bath of salt solution at 50 degrees C. This high pressure appeared to be the most important factor in the procedure. Injections at the expected coronary blood pressure of 110 to 120 mm. Hg. did not penetrate into

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the valves. When, however, the higher pressure was applied, many more small vessels became filled. The injection was held at this stage for half an hour. At the end of this time, while the pressure was maintained at 190 mm. Hg., the warm bath surrounding the heart was replaced with ice-water. When the gelatin had solidified in the coronary arteries, the cannulæ were disconnected and the heart cut open to remove the carmin gelatin collected in the auricles and ventricles. The opened heart was then placed in 10 per cent formalin to harden the gelatin in the small vessels. After 48 hours or longer, the valves were dissected, the atrioventricular rings being removed with the tricuspid and mitral valves, and strips of the pulmonary artery and aorta with the semilunar valves. Vessels could be seen in the upper portions of the atrioventricular valves and sometimes in the chordæ tendineæ at this stage. In order to render the whole vascular network readily visible, the valves were dehydrated in 95 per cent alcohol, cleared in a mixture of 2 parts of oil of wintergreen and 1 part of benzol. In valves rendered transparent in this manner, the vessels could be studied to greatest advantage with the binocular microscope.

In the pig, the artioventricular and semilunar valves and the chordæ tendineæ are well supplied with blood-vessels. They differ only in numbers from the vessels of the valves of the human heart and will not be described here in detail.

Blood-Vessels of the Valves of the Human Heart.

Atrioventricular Valves.—The human hearts used for these injections were carefully selected normal hearts, obtained from autopsies in the Pathological Department of The Johns Hopkins Hospital. Fourteen hearts were injected. These were taken from human subjects of the following ages: 1 to 10 years, six hearts; 10 to 20 years, two hearts; 20 to 30 years, two hearts; 30 to 60 years, four hearts. In some of these, only irregular groups of vessels and long, delicate arterioles extending to the line of closure of the valves were shown by the injection. In three hearts fairly complete injections were obtained. The following description is based upon these injections:

The *tricuspid and mitral valves* receive arterioles from the annular branches of the right and left coronary arteries, as these pass through the region of the annulus fibrosus at the atrioventricular junction. These small arteries to the valves are not derived from the vessels which supply the auricular musculature, but are distinct branches

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from the annular arteries passing directly into the valves. The general distribution of these vessels is shown by Fig. 1, which is a photograph of the mitral valves of a woman, aged 21, who died after an

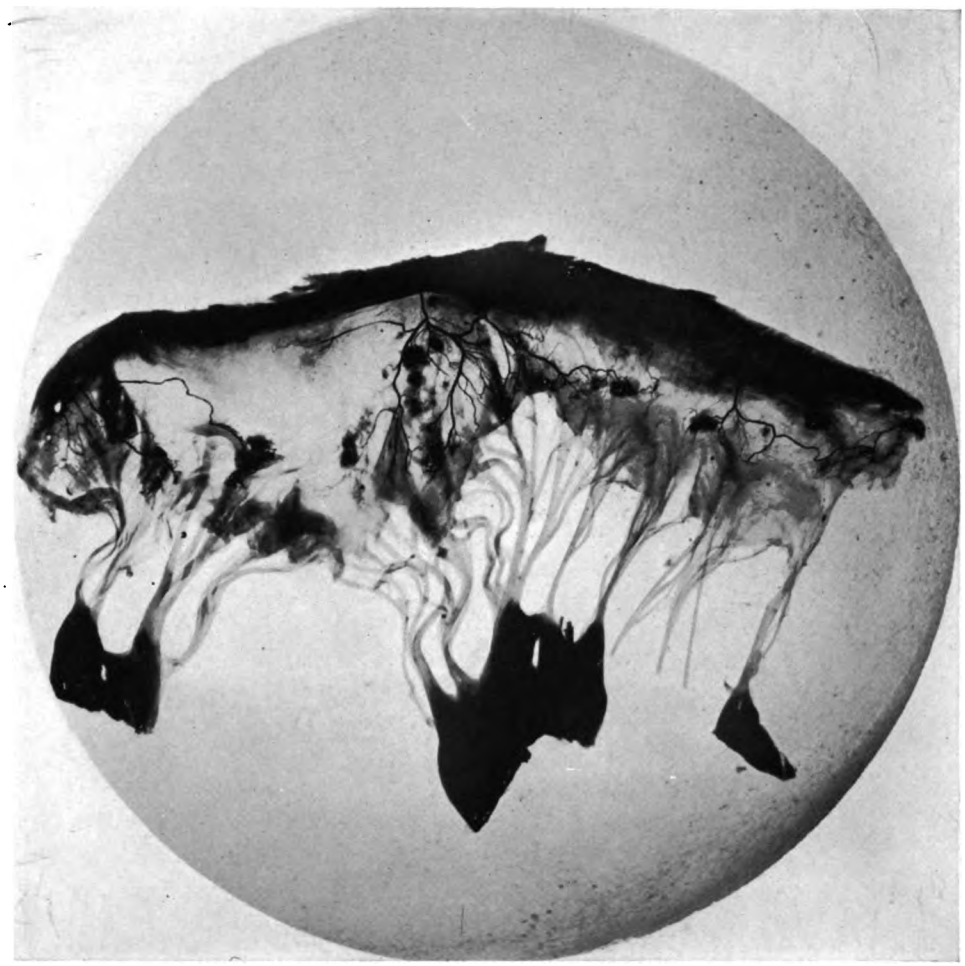

Fig. 1.—Mitral valve from human heart injected with carmin gelatin, showing the normal arrangement of vessels in the atrioventricular valves. Photograph of cleared specimen, enlarged three times.

operation for exophthalmic goitre (Autopsy No. 4609). Fig. 2 is a drawing of these vessels, made directly from the photograph of the specimen. The chief arteries to the valve branch from the annular

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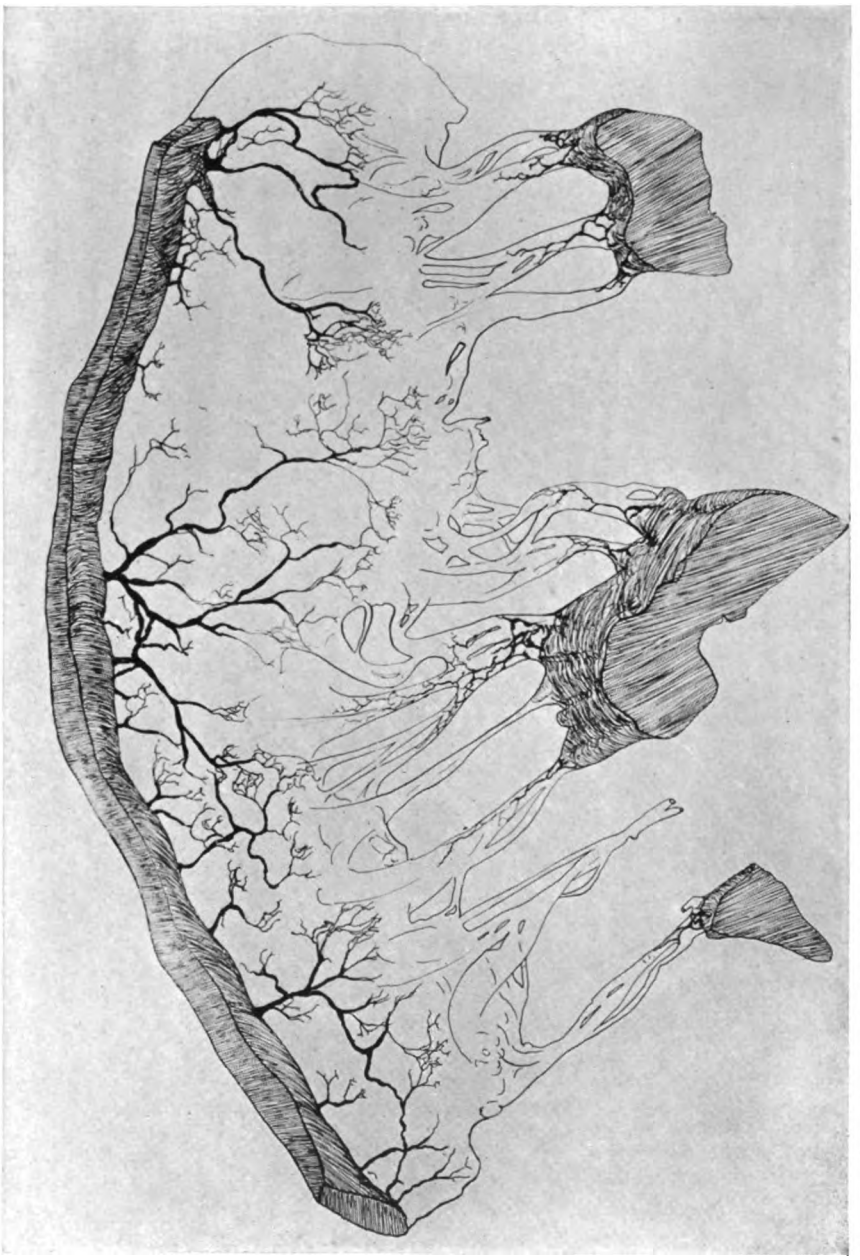

FIG. 2.—Drawing from photograph of injected vessels of mitral valve of human heart. This shows a few delicate blood-vessels in the chordæ tendineæ which are not visible in the photograph.

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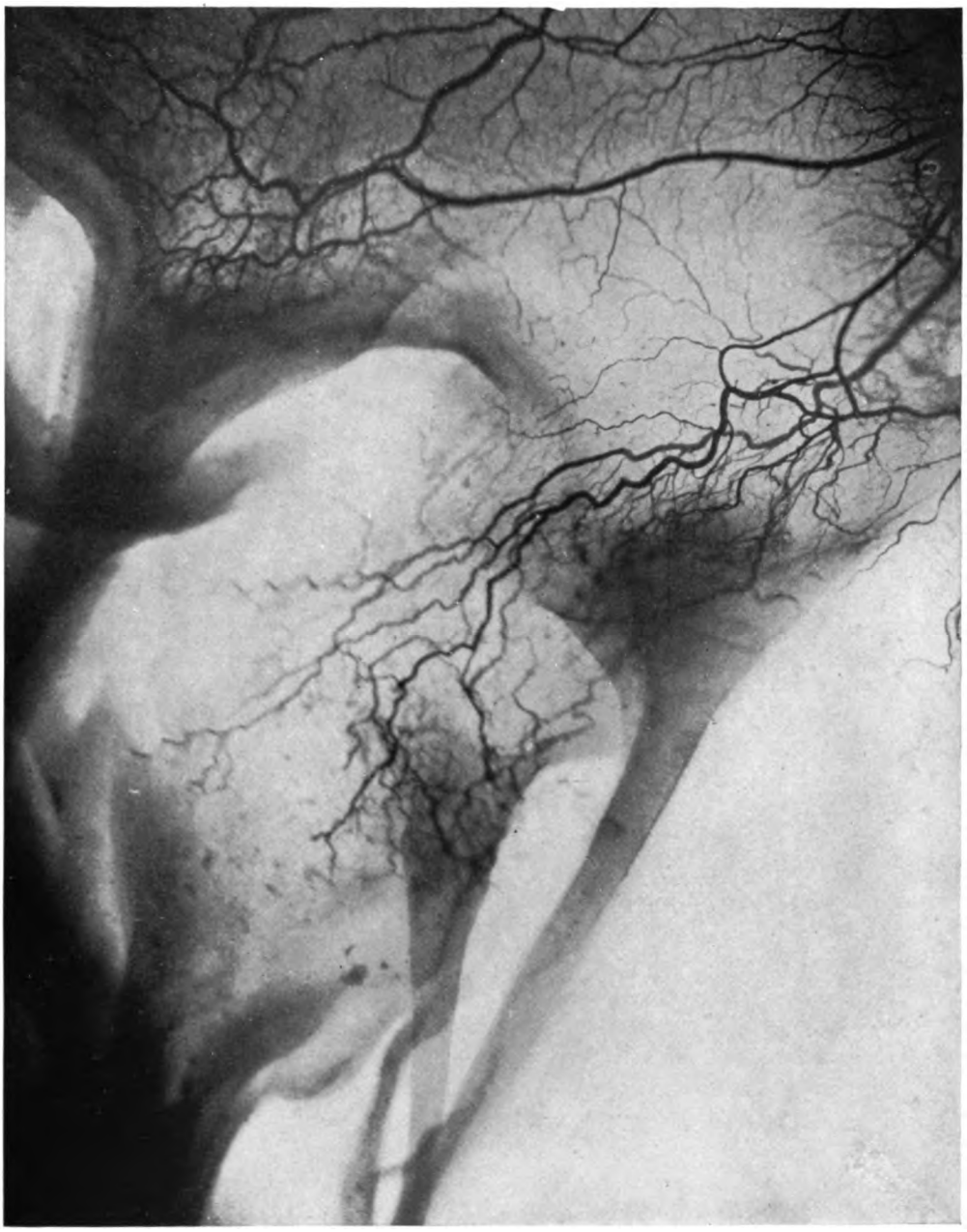

FIG. 3.—Enlarged photograph of distribution of blood-vessels along the line of closure of mitral valve shown in Fig. 1.

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artery at widely separated intervals. These points of entrance are almost directly above the papillary muscles, and the vessels pass down the valve in the thickened portion above the insertions of the chordæ tendineæ. During this downward course, the arteries give off small lateral branches which ramify as delicate arterioles in the upper third of the membranous portion of the valve. When the thickened area of the line of closure of the valve is reached, the arteries undergo multiple branching, forming tufts of vessels in this region (Fig. 3). From the terminal arterioles many small vessels anastomose, almost forming glomerular tufts and loops. In this region the capillaries form abundant anastomoses. Only occasional strands of small vessels pass from the line of closure to the free margin of the valves. No vessels were found passing from the valves to the chordæ tendineæ.

In the upper portions of the valves distinct differences between the vessels may be seen, differentiating arteries from veins. The arteries have irregular edges, with the lumen constricted in some places and expanded in others. A definite constriction occurs wherever the artery branches. The veins, on the other hand, have a smooth contour, and are not so deeply colored by the injection. These features are shown in Fig. 4, which is a composite drawing made by Mr. Max Brödel, representing in a semidiagrammatic manner the completely injected regions of several specimens.

Chordæ Tendineæ.—In the human heart, the vascularity of these structures is slight. The arteries are derived from the branches of the descending rami of the coronary arteries which supply the papillary muscles. These vessels form a subendothelial plexus around the bases of the chordæ tendineæ, and from this plexus delicate strands of vessels can be seen passing up along the chordæ tendineæ almost to their insertions in the valves. Nearly all of these vessels in the chordæ lie just beneath the endothelium. Some, however, are situated in the center of the chordæ.

The chordæ tendineæ of the pig's heart have an abundant supply of blood-vessels. As these have not been previously described, they are shown here in the following photograph (Fig. 5).

Semilunar Valves.—The blood-vessels of the aortic and pulmonary valves arise from two sources, one of which is the vasa vasorum of the arteries, the other the vessels of the auricular endocardium. Injections of the semilunar valves were successful in only three normal hearts. The pulmonic were more easily injected than the aortic, from the fact

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Fig. 4.—Semi-diagrammatic drawing of typical areas from several injected specimens of valves from human hearts. (By Mr. Max Brödel.)

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FIG. 5.—Photograph of injected blood-vessels in the chordæ tendineæ of the pig's heart. Enlarged eight times.

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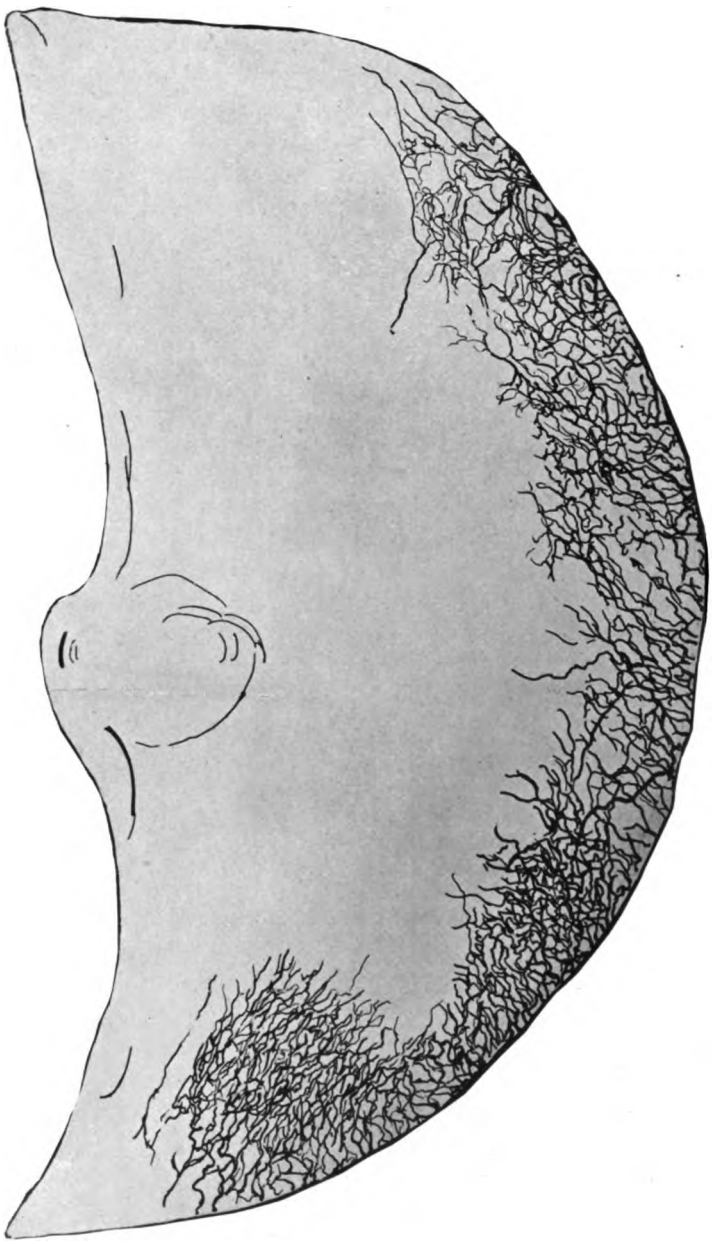

FIG. 6.—Pulmonic valve from human heart, showing the typical vascular arrangement of the semilunar valves. This drawing was made directly upon a photograph of the specimen.

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that the insertion of the cannulæ into the sinuses of Valsalva compresses the blood-vessels of the aortic valves. A drawing made upon a photograph of a specimen of an injected pulmonic valve is shown in Fig. 6. In this, the few delicate vessels, which arise from the vasa vasorum where the cusps are attached to the wall of the artery and penetrate the valve for a short distance along its line of closure, are not shown. The vessels going to the valve from the auricular endocardium form a hedge-like plexus in the base of the cusp, and from this plexus delicate vessels pass upward for a distance of about a half of the extent of the valve. No vessels were seen in the thin central portion of the valve or in the noduli arantii.

Summary.

These studies may be summarized as follows:

1. By the injection of carmin gelatin under a pressure of 160 to 190 mm. Hg. into the coronary arteries, blood-vessels are demonstrable in the valves of the normal human heart.

2. The atrioventricular valves receive distinct branches from the annular divisions of the coronary arteries. These vessels pass into the valves at the thickened regions above the insertion of the chordæ tendineæ and ramify chiefly along the line of closure of the valves. Arteries, veins and an anastomosing capillary bed are recognizable in these locations.

3. The chordæ tendineæ receive a few small arterioles from the vessels of the papillary muscles. These traverse the chordæ tendineæ chiefly beneath the endothelium covering these structures.

4. The semilunar valves receive a definite blood supply from the vasa vasorum of the pulmonary artery and aorta, and from the endocardial vessels of the auricles.

5. These vessels afford a definite anatomical basis for the conception that endocarditis may be embolic in its origin.

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EQUILIBRIA IN PRECIPITIN REACTIONS.

THE CO-EXISTENCE OF A SINGLE FREE ANTIGEN AND ITS ANTIBODY IN THE SAME SERUM.

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The vagueness of the terms of serology connotes the difficulties with which the describers of this new knowledge have had to contend. Unable to use simple and definite chemical substances, and without the guidance of any general theory, they have had to employ mass-adjectives to describe the reactions of a serum as a whole, and have gathered great numbers of observations without any plan for their co-ordination. Whenever, therefore, it is possible to rework former experiments by substituting known factors in place of unknown mixtures, that work should be undertaken. Quantitative data will be obtained through these studies which will eventually allow serology to find a place in either chemistry, physics, or—what seems almost self-evident—in physical chemistry. The colloidal state of matter has afforded so many analogies to the reactions of serology that the terms of colloidal-chemistry have already been applied with uncritical facility by immunologists to reactions that have not yet been studied with quantitative accuracy sufficient to indicate their true nature. The systematic attempt, however, to prove or disprove these colloidal analogies in serology will undoubtedly result in a unifying conception of the principles of the reactions of immunity.

The precipitation of protein by specific sera has many analogies with colloidal reactions, and this phenomenon lends itself readily to investigation simplified by the use of at least a single pure substance. Zinsser[1] has repeatedly emphasized the colloidal phases of the precipitin reaction, and recently Weil[2] has reworked the subject, using crystallized egg albumin as the antigen. One of the phases of the precipitin reaction, which has engaged particular attention, is that in which the precipitinogen and precipitin occur simultaneously, but

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ununited in the same serum. This is easily demonstrable when whole serum or a mixture of proteins is used as the antigen. Weil, however, using crystalline egg albumin as the antigen, was unable to demonstrate the co-existence of free antigen and antibody in the same serum. It is of considerable theoretical importance to confirm this finding. The results obtained by Weil are so little in accord with expectations based upon chemical or colloidal theories, that it was considered advisable to repeat the experiments on precipitin reactions with crystalline egg albumin. The following studies, therefore, were carried out under the direction of Dr. Zinsser with some modifications of recent work on this reaction.

Historical Review.

In 1902, Linossier and Lemoine,[3] Ascoli,[4] and Eisenberg[5] noticed that when foreign serum was injected into rabbits in large doses the sera of these animals contained both antigen and antibody. They used whole sera as antigens. To demonstrate the simultaneous presence of free precipitable substance and its precipitant in the same serum, fractions of the serum were tested first for antigen, by adding another antiserum, and secondly for precipitin by adding an homologous antigen. Gay and Rusk[6] have described the same phenomena, and by showing that the sera do not fix complement, although they contain antigen and antibody, they have furnished additional evidence of the ununited state of the substances.

Von Dungern[7] confirmed these findings, but explained them according to a different hypothesis. He showed that whole serum consists of a number of protein complexes, all of which cause the formation of precipitin in the immunized animal. One portion of the protein mixture may have more antigenic properties than another, as a result of which partial precipitins of various strengths are produced for the whole serum. Von Dungern believed that these complex antigens and multiple antibodies reacted irregularly in such a way that while the supernatant fluid of a precipitin test would contain free antigens found in part in the original serum, together with precipitins capable of flocculating the original serum, yet the anti-substances in the supernatant fluid were not strictly homologous, and hence would not react with each other. His extensive experiments have had great influence upon subsequent opinions. He worked, however, entirely with multiple

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antigens, and furnished only inferences and analogies for the precipitin reactions with pure proteins.

At first glance, it would seem as if the experiments in the precipitation of casein with lactoserum, reported by P. T. Müller,[8] were evidence that with purified antigens the phenomenon of Linossier and Lemoine did not occur. The supernatant fluids, after his precipitin reactions, never contained free antigen along with antibody. His experiments, however, are not relevant to the results of precipitin reactions with purified protein. Müller used whole milk as his "casein," obviously a multiple-antigen, and the degrees of dilution used in the tests leave such large gaps that the zone in which antigen and antibody co-exist ununited might have been overlooked.

The recent important work on the subject is that reported by Weil[9] in 1916. He confirms all the previous observations on the co-existence of free antigen and antibody in the supernatant fluids of precipitin tests, when the whole serum, raw egg-white, or any mixed protein is used. With purified egg albumin as antigen, the results were entirely different. He says: "If this antigen is mixed in graded proportions with the serum of a rabbit immunized thereto, and the resulting precipitates are removed by centrifugation, the supernatant fluid never contains both antigen and antibody; either one is present alone." The protocols of Weil's precipitin tests allow him to draw sharp conclusions between the effect of 0.005 c. c. and 0.004 c. c. of the antigen, a delicacy of reaction which not all workers have been able to attain. The crystalline egg albumin, prepared for him by Coca, was certainly as pure as it is possible to obtain this substance. It is not stated whether tests for anaphylactic reactions were carried out with this particular preparation to determine whether it was thereby free from antigen-complexes, which cause reactions in animals sensitized with egg globulin. Weil states, however, that he and Coca[9] found that "if albumin and egg globulin were separated by chemical means, and different rabbits were immunized to each substance, the resulting immune sera reacted powerfully with its own antigen and very weakly with the other antigen." This anaphylactic interrelation of egg proteins will be discussed later. It is significant here to note the apparent discrepancy between the results of these precipitin tests and anaphylactic reactions, although one antigen was used which admittedly gives some anaphylactic reaction with other proteins.

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Experimental Studies.

Sera capable of precipitating egg albumin were prepared by immunizing rabbits with intravenous injections of this protein. By varying the proportions of immune serum and solution of egg albumin in the precipitin tests, zones of dilution were obtained in which tests for free antigen and free antibody could be made. In addition, by testing the sera of immunized rabbits at certain intervals after the injection of albumin, the proportions and duration of circulating antigen and antibody could be studied.

The important material for these experiments is the antigen. Attempts to use casein failed because of the confusing precipitates caused by the calcium salts required in the tests with this protein. In some experiments edestin from hempseed was used, from a preparation made by Dr. Harris of the Connecticut Agricultural Station. The results with this protein were definite. Because, however, of the scanty solubility of edestin, work with it is somewhat difficult. Crystalline egg albumin was found to be most suitable for these studies. This substance was prepared under the direction of Mr. Balls of the Department of Physiological Chemistry, according to the method of Hopkins and Pinkus.[19] The whites of freshly laid eggs were carefully precipitated with ammonium sulphate, and the albumin from these was recrystallized three times. The solution of protein was dialyzed under toluol in the ice-box, to free it as much as possible from ammonium sulphate and acetic acid. The albumin was then dried in vacuo to a white glistening powder. The Zsigmondy "gold-number" for the preparation was 8, showing the usual protective value of pure egg albumin as a colloid. This preparation met the requirements for pure crystalline egg albumin, and was probably as pure as it is possible to obtain a protein of this nature.

Anaphylactic tests were made in the hope of showing that this preparation of egg albumin was free from globulin, or substances which have no antigenic properties like globulin. Egg globulin was prepared from the first fraction of egg white, precipitated with a half saturation with ammonium sulphate. A solution of the precipitate was dissolved in distilled water and dialyzed against distilled water until the globulin began to flocculate. This material was centrifuged, and the precipitate taken up in 10 per cent NaCl. This formed a turbid emulsion, free, however, from large particles. One series of guinea-

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pigs, weighing 250 gm., were sensitized by intravenous injections of varying amounts of crystalline egg albumin; another series by intravenous injections of egg globulin. After an interval of 26 days the animals were reinjected with protein, according to the following protocol:

TABLE I.

Anaphylactic reactions with ovalbumin and ovoglobulin from the same eggs.

Guinea-pigs weighing from 200 to 250 gm. were injected intravenously with solutions of the proteins on July 13, 1916.

Second injection on August 7th; after an interval of 26 days.

Separate syringes and needles were used for each protein.

A. ANIMALS SENSITIZED TO CRYSTALLINE OVALBUMIN.

Guinea-pig.	Sensitizing dose.	Interval.	Second injection.	Result.
	gm. albumin.		*gm. albumin.*	
949	0.002	26 days.	0.1	Convulsions. Died.
951	0.002	26 "	0.2	Convulsions. Died in 2 hrs.
962	0.001	26 "	0.1	Typical anaphylaxis. Died in 3 min.
963	0.001	26 "	0.1	Convulsions. Died in 3 min.
964	0.0005	26 "	0.1	Violent convulsions. Died in 2 min.
			gm. globulin.	
953	0.002	26 "	0.1	Convulsions. Died in 3 min.
955	0.002	26 "	0.1	Died in 30 min.
956	0.001	26 "	0.002	Diarrhea. Survived.
952	0.001	26 "	0.002	Sneezing, coughing. Survived.

B. ANIMALS SENSITIZED TO OVOGLOBULIN.

Guinea-pig.	Sensitizing dose.	Interval.	Second injection.	Result.
	gm. globulin.		*gm. globulin.*	
950	0.004	26 days.	0.1	Convulsions. Died in 1 min.
960	0.002	26 "	0.002	Convulsions. Died in 1 min.
965	0.002	26 "	0.002	Convulsions. Paralysis hind legs. Died in 2 min.
947	0.001	26 "	0.002	Cough. Survived.
959	0.001	26 "	0.002	Convulsions. Died in 2 min.
946	0.0005	26 "	0.002	Convulsions. Died in 2 min.
			gm. albumin.	
948	0.002	26 "	0.1	Cough, etc. Survived.
954	0.002	26 "	0.1	Sneezing, dyspnea. Survived.
961	0.001	26 "	0.1	Sprawling, twitching. Survived.
957	0.001	26 "	0.1	Cough. Survived.
958	0.0005	26 "	0.1	Cough, etc. Survived.

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The results of the experiments summarized in Table I, show that preparations of egg albumin and egg globulin have a common antigenic factor, capable of producing mutual anaphylactic reactions. They confirm the statements of Wells [21] and Osborne,[22] who, after a long series of experiments, concluded that "in spite of the most careful separation of egg globulin from egg albumin by means of ammonium sulphate precipitation, the resulting preparations each react almost as well against each other as against itself." Weil and Coca [9] report a somewhat similar experience with crystalline egg albumin, when injected into animals sensitized to egg globulin. These reactions have been considered in detail in order to determine whether or not the anaphylactic test is a valid criterion of the purity of a protein, and in particular whether the anaphylactic interreactions of egg globulin and egg albumin exclude the latter from use as a single pure antigen. Crystalline egg albumin is acknowledged to be a pure protein.[12, 23] "Egg globulin, however, probably consists of ovomucin and ovalbumin admixed in indefinite proportions." [23] The impurity of the "globulin" renders the anaphylactic reactions without significance. In the protocols of Table I, it is seen that the albumin-globulin reactions are much weaker than those caused by the injection of the specific proteins into a sensitized animal. This undoubtedly indicates that the globulin preparation contained ovalbumin. Belief in the individuality of the crystalline egg albumin as an antigen rests upon its chemical characteristics.

Accepting, therefore, purified edestin and ovalbumin as single antigens, the following experiments were conducted upon their specific precipitin reactions.

EXPERIMENT 1.

Edestin as Antigen.

To show the co-existence of edestin and its precipitin in the serum of an immunized rabbit. April 15-18, 1916. Serum from Rabbit 139, immunized to edestin, obtained one hour after an intravenous injection of 12 c. c. of 0.02 solution of edestin. This serum was kept for three days in the ice-box before being tested for its content of antigen and antibody. Serum from Rabbit 422 also immunized to edestin, having a precipitin titer of 1-4000.

These sera were mixed in various proportions. The diluent used was a mixture containing NaCl 0.9 per cent and Na_2CO_3 0.05 per cent in order to keep the edestin in solution.

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QUANTITIES EXPRESSED IN CUBIC CENTIMETERS.

Tube.	Serum 189.	Edestin.	Chloride carbonate solution.	Serum 422.	Precipitate.		
					Ring.	½ hr. 37° C.	24 hrs. in ice-box.
For precipitin							
1.....	Undiluted 0.2	0.2	0.5	.....	±	+	+
2.....	Dil. 1–5 0.2	0.2	0.5	.....	0	++	++
For antigen							
3.....	Undiluted 0.2	.....	0.5	0.2	+	++	++
4.....	Dil. 1–100 0.2	.....	0.5	0.2	++	+	+
5.....	1–1000 0.2	.....	0.5	0.2	±	±	±
Control							
6.....	Undiluted 0.2	.....	0.7	.....	0	0	0
7.....	.....	.....	0.7	0.2	0	0	0
8.....	.....	0.2	0.7	.....	0	0	0
9.....	.....	0.2	0.5	1–4000 0.2	±	+	+

Tubes 1 and 2 show that this serum contained free precipitin. Tubes 3, 4 and 5 show that free antigen was also present.

EXPERIMENT 2.

EDESTIN AS ANTIGEN.

April 20. Various quantities of *edestin* added to its antiserum to find zone of dilution *in vitro* in which antigen and antibody occur in supernatant fluids after the primary precipitin reaction.

Serum from Rabbit 422, immunized to edestin having a titer of 1-2000.

Edestin 0.02 per cent mixed in various proportions with undiluted serum No. 422, as follows, quantities being expressed in cubic centimeters.

Tube.	Serum 422.	Edestin 0.02% sol.	Chloride carbonate mixture.	Precipitate after 24 hrs. in ice-box.	Supernatant fluids for antigen 0.2 c. c. supernat. 0.8 c. c. serum 422.	For precipitin 0.2 c. c. supernatant. 0.8 c. c. edestin sol.
1	0.2	2	.....	++	++++	0
2	0.2	1	.....	++	++	±
3	0.2	0.5	0.3	+++	++	±
4	0.2	0.2	0.6	+++	+	+
5	0.2	0.1	0.7	++	Trace.	+
6	0.2	0.01	0.8	+	?	+
7	0.2	0.001	0.8	+	0	++
8	0.2	0.0001	0.8	±	0	++
9	0.2	0.00001	0.8	0	0	++
Controls.						
10	0.2	.....	0.3	0	.....	++
11	.....	0.2	0.3	0	++	0

The overlapping shaded areas in the above chart indicate the zone in which antigen and precipitin are present in these fluids.

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EXPERIMENT 3.

Crystalline Egg Albumin as Antigen.

To show the co-existence of antigen and antibody in circulation of an immune animal. June 2, 1916. Serum from Rabbit 210, immunized to crystalline egg albumin, having a titer of 1-5000 before last injection of antigen.

10.45 a. m. 3 c. c. of 5 per cent solution of crystalline egg albumin injected intravenously.

In Rabbit 210. 11.30 a. m. Bled from carotid 15 c. c.

At 3 p. m. tests were carried out as follows:

Tube.		Serum No. 210 A before injection.	Serum No. 210 B after injection.	Crystalline egg albumin 5% solution.	Normal salt solution.	Normal rabbit serum.	Precipitate after ½ hr. at 37° C.
For antigen in serum 210 A	1..	0.2	0.2	.....	.....	.....	++++
For precipitin in 210 B	2..	.....	0.2	0.2	.....	.....	+++
	3..	.....	0.2	1–10 0.2	.....	.....	++
	4..	.....	0.2	1–100 0.2	.....	.....	0
Controls	5..	0.2	.....	.....	0.2	.....	0
	6..	0.2	.....	.....	.....	0.2	0
	7..	.....	0.2	.....	0.2	.....	0
	8..	.....	0.2	.....	.....	0.2	0
	9..	.....	.....	0.2	0.2	.....	0
	10..	.....	.....	0.2	.....	0.2	0
	11..	.....	.....	.....	0.2	0.2	0

Tube 1 shows that the serum of Rabbit 210 contained antigen ununited with its antibody 45 minutes after an injection of crystalline egg albumin. Tubes 2, 3 and 4 show that during the time free precipitin was still present in the blood of the immune animal.

Several experiments like this were conducted. As the protocols are identical, they are omitted here. By testing the sera of rabbits immunized to egg albumin at different periods after the injection of albumin, it was found that antigen and antibody are present separately in the circulating blood for about 48 hours.

EXPERIMENT 4.

Crystalline Egg Albumin as Antigen.

June 16, 1916. Various quantities of crystalline *ovalbumin* were added to its antiserum to find the zone of dilution *in vitro* in which antigen and antibody occur in the supernatant fluids after the primary precipitin reactions.

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Serum from Rabbit 210 immunized to crystalline egg albumin, having a titer of 1-10,000.

Crystalline egg albumin 5 per cent in normal salt solution added in diminishing amounts to undiluted serum No. 210, according to the following table.

Quantities are expressed in cubic centimeters.

Tube.	Serum No. 210 undiluted.	Crystalline egg albumin 5%.	Normal salt solution.	Precipitate after 18 hrs. in ice-box.	Supernatant fluids.	
					For antigen 0.2 c. c. supernatant. 0.2 c. c. serum 210.	For precipitin 0.2 c. c. supernatant. 0.2 c. c. cryst. albumin diluted 1-10.
1....	0.5	0.05	0.25	++	+++	+
2....	0.5	0.01	0.25	+++	++	+
3....	0.5	0.005	0.25	+++	++	+
4....	0.5	0.001	0.25	++++	+	++
5....	0.5	0.00075	0.25	+++	±	++
6....	0.5	0.0005	0.25	++	0	++
7....	0.5	0.0001	0.25	+	0	+++
8....	0.5	0.00005	0.25	±	0	+++
Controls.						
9....	0.5	.....	0.25	0	0	++++
10....	.....	.5	0.25	0	+	0
11....	.....	.5	Normal rabbit serum 0.25	0	+	0

The overlapping shaded areas in the above chart show the zone in the supernatant fluids in which free antigen and antibody (crystalline egg albumin and its precipitin) defintely co-exist.

In many of the precipitin reactions with crystalline egg albumin, the maximum of precipitation occurred only when the albumin solution was diluted 500 or 1000 times. This phase of the precipitin reaction is commonly known as the "prozone," and is most readily explained as a phenomenon of colloidal relationships. In this particular case it seemed desirable to investigate the inhibition of precipitation effected by the albumin preparation, to relate it, if possible, to the protective influence exerted by the emulsoid on a sensitive gold sol. To show this effect, the following experiment was performed:

EXPERIMENT 5.

To show the protective action of a solution of crystalline egg albumin upon the precipitation of human serum by its specific antiserum. To the serum from Rabbit 447 having a titer of 1 to 10,000 against human serum, various quantities of a 5 per cent solution of crystalline egg albumin were mixed with human serum. After one-half hour antihuman serum from

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Rabbit 447 was added to this mixture as follows. The gold number of this preparation of egg albumin was 8.

Tube.	Human serum.	Antihuman serum.	Crystalline egg albumin 5% sol.	Normal salt.	Precipitate ½ hr. at 37° C.
1.....	0.2	0.2	.....	0.2	++++
2.....	0.2	1–5 dil. 0.2	.....	0.2	+++
3.....	1–100 0.2	1–5 0.2	.....	0.2	++
4.....	1–1000 0.2	1–5 0.2	.....	0.2	+
5.....	1–5000 0.2	1–5 0.2	.....	0.2	+
6.....	1–10,000 0.2	1–5 0.2	.....	0.2	0
7.....	0.2	0.2	0.2	.....	++++
8.....	0.2	1–5 0.2	0.2	.....	++
9.....	1–100 0.2	1–5 0.2	0.2	.....	++
10.....	1–100 0.1	1–5 0.1	0.2	0.2	±
11.....	1–100 0.1	1–5 0.1	0.4	.....	0
Controls 12.....	0.2	.....	.....	0.2	0
13.....	0.2	.....	0.2	.....	0
14.....	.....	0.2	0.2	.....	0
15.....	.....	0.2	.....	0.2	0

These tests (tubes 7-11) show that the presence of sufficient egg albumin prevents the flocculation of human serum by its antiserum. This effect of the solution of egg albumin is in accord with its well-known protective action on other colloids, particularly its protection of a sensitive gold-sol. against precipitation by electrolytes. Its protective action in the above tests is obviously stronger than that exerted by serum and may explain the long "prozones" commonly found in precipitin reactions with solutions of crystalline egg albumin.

The hypothesis of von Dungern is insufficient to explain the fact that a serum containing both antigen and antibody, though clear at first, undergoes spontaneous precipitation upon long standing.[1] As the precipitation progresses the amounts of antigen and antibody gradually diminish. This phenomenon is a matter of common observation, when the sera of animals immunized to a mixture of proteins are studied at successive intervals after an injection of the proteins used as antigen. Since it was shown by Experiments 1 and 3, of these studies, that a simple antigen, such as edestin or crystalline egg

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albumin remains ununited with its homologous precipitin in the circulation of an immune rabbit for at least 24 hours after the last injection of the protein, a serum was readily obtained in which the slow spontaneous union of a single antigen with its antibody could be observed. This series of tests were carried out as follows:

EXPERIMENT 6.

Spontaneous precipitation in a serum containing antigen and antibody (crystalline egg albumin and its precipitin).

July 27, 1916. Rabbit 941 immunized to crystalline egg albumin, having a serum with a titer of 1 to 25,000, was injected intravenously with 3 c. c. of a 5 per cent solution of crystalline egg albumin. One hour later blood was drawn aseptically into sterile tubes. Serum obtained from this was divided into several lots and stored in sterile tubes in the ice-box. Titrations for antigen and antibody were made as follows; quantities being expressed in cubic centimeters:

Tube.	Serum 941 after injection.	Serum 941 before injection.	Crystalline egg albumin 5% solution.	Normal salt.	Normal rabbit serum.	Precipitate.	
						½ hr. at 37° C.	24 hrs. in ice-box.
For antigen.							
1	0.2	0.2	.....	.....	.....	+++	.....
For precipitin.							
2	0.2	.....	1–10 0.2	.....	.....	++	++
3	0.2	.....	1–100 0.2	.....	.....	+	+
4	0.2	.....	1–500 0.2	.....	.....	+	+
5	0.2	.....	1–1000 0.2	.....	.....	+	+
6	0.2	.....	1–5000 0.2	.....	.....	+	+
7	0.2	.....	1–10,000 0.2	.....	.....	0	±
Controls.							
8	0.2	.....	.....	0.2	.....	0	Slight precipitate (spontaneous)
9	.....	.....	1–10 0.2	.....	0.2	0	0
10	.....	.....	1–10 0.2	0.2	.....	0	0
11	0.2	.....	.....	.....	0.2	0	0
12	.....	0.2	.....	.....	0.2	0	0
13	.....	0.2	1–25,000 0.2	.....	.....	+	+

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Tube 1 shows that the serum contained a considerable amount of antigen, while the tubes 6 and 7 show that the precipitin titer of the same serum equalled 1 to 10,000. Tubes 8 to 13 were used to show that no non-specific precipitation occurred in any of the components of the primary reaction. In the subsequent tests, this series of controls was repeated invariably. The results were always as anticipated, and they will be omitted in detail from the following protocols.

The batches of serum 941 kept in the ice-box showed definite spontaneous precipitation at the end of 24 hours.

July 28, titrations of the antigen and antibody content of this serum carried out as follows:

Tube.		Serum 941 after injection.	Serum 941 before injection.	Crystalline egg albumin 5%.	Precipitate.	
					½ hr. at 37° C.	24 hrs. in ice-box.
For antigen	1.....	undil. 0.1	0.1	.....	++	++++
	2.....	1–10 0.1	0.1	.....	+	+++
	3.....	1–100 0.1	0.1	.....	+	++
	4.....	1–250 0.1	0.1	.....	+	+
	5.....	1–500 0.1	0.1	.....	0	+
	6.....	1–1000 0.1	0.1	.....	0	0
For precipitin	7.....	undil. 0.1	.....	1–1000 0.1	+	+
	8.....	0.1	.....	1–5000 0.1	+	±
	9.....	0.1	.....	1–10,000 0.1	0	0

This series of tests shows that the quantity of antigen present in serum 941 (after injection) was sufficient to give a visible reaction when diluted 500 times. At the same time the precipitin titer of this serum containing free antigen was 1 to 1000. In the previous 24 hours, however, while spontaneous precipitation had occurred in this serum, the precipitin titer decreased from 1 to 5000 to 1 to 1000.

Spontaneous precipitation continued, and at the end of 48 hours the following proportions of egg albumin and its precipitin were found to be present.

July 29, 1916. Serum 941 titrated as follows:

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Tube.		Serum 941 after.	Serum 941 before.	Albumin solution.	Precipitate.	
					½ hr. at 37° C.	24 hrs. in ice-box.
For antigen	1.....	0.1	0.1	.....	++	+++
	2.....	1–10 0.1	0.1	.....	+	++
	3.....	1–100 0.1	0.1	.....	+	+
	4.....	1–250 0.1	.....	.....	0	+
	5.....	1–500 0.1	.....	.....	0	0
For precipitin	6.....	0.1	.....	1–500 0.1	+	+
	7.....	0.1	.....	1–1000 0.1	0	0
	8.....	0.1	.....	1–5000 0.1	0	0

On July 31, 96 hours after the serum had been obtained, the tubes were turbid with considerable flocculated material in the sediment. The turbidity disappeared on warming the serum, but the sediment remained, giving evidence of the specific nature of this spontaneous precipitate. Titration of the serum at the end of 96 hours gave the following values for its content of free antigen and antibody.

Tube.		Serum 941 (after).	Serum 941 (before).	Albumin solution.	Precipitate.	
					½ hr. at 37° C.	24 hrs. in ice-box.
For antigen	1.....	0.1	0.1	.....	+++	+++
	2.....	1–10 0.1	0.1	.....	++	++
	3.....	1–150 0.1	0.1	.....	+	+
	4.....	1–200 0.1	0.1	.....	+	+
	5.....	1–300 0.1	0.1	.....	0	0
For precipitin	6.....	0.1	.....	1–100 0.1	±	+
	7.....	0.1	.....	1–350 0.1	0	0

This shows that during the course of spontaneous precipitation in the serum both egg albumin and its precipitin became decreased. At the end of 96 hours the antigen titer had fallen to 1 to 200 and the precipitin titer to 1 to 100.

Subsequent titrations were carried out to follow the decrease of these antisubstances coincident with progress of spontaneous precipitation in the serum.

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At the end of 144 hours the serum no longer contained precipitin, while the antigen titer had decreased to 1 to 100.

At the end of 196 hours the precipitin was still zero, while the antigen titer remained constant at 1 to 100.

The results of these titrations of the supernatant serum during spontaneous precipitation may be graphically represented by the following curves. (Fig. 1.)

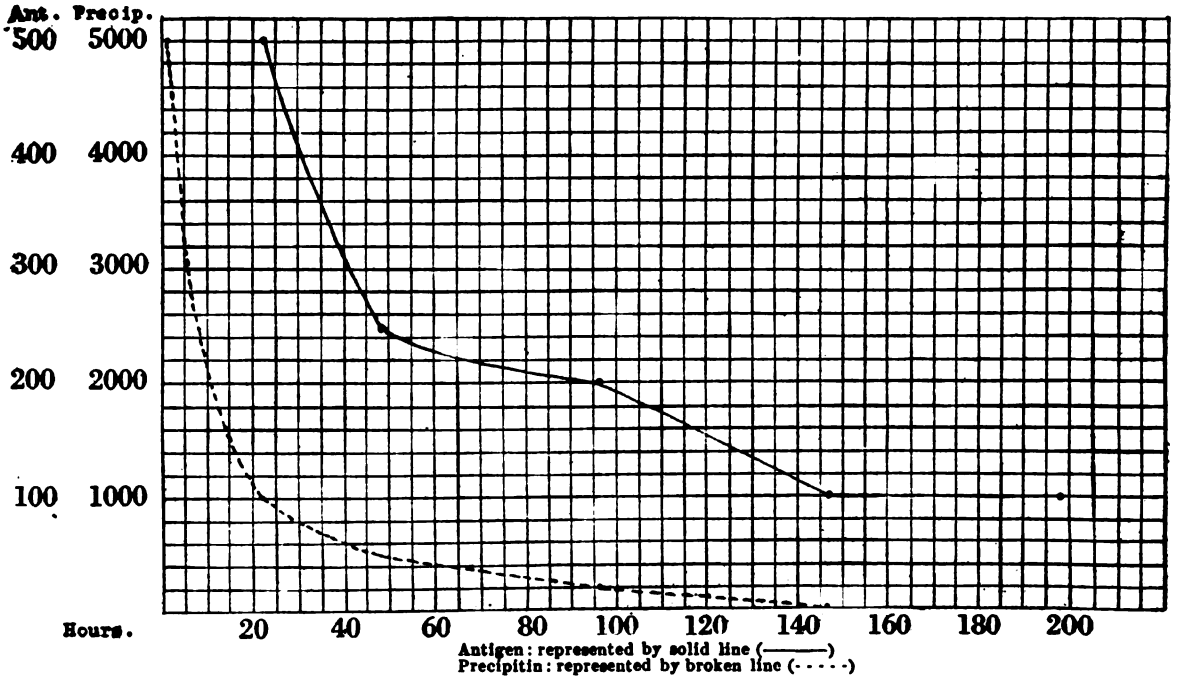

FIG. 1.

The graph of the observed amounts of antigen and antibody remaining dissociated in the supernatant fluid of this precipitin reaction suggests at once that the process has taken place according to a definite law. From the data at hand, as the amounts of antigen and precipitin are stated here only in terms of the dilution of mixtures whose protein content was not accurately estimated, it is not possible to analyze the curve in detail. Experiments are being undertaken, therefore, to determine quantitatively the mutual relationships of the factors of this reaction. While, however, calculations are not possible which would reveal the nature of this reaction, it is permissible to point out that the

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curve is not unlike that of some colloidal precipitations. In this case the amount of precipitate together with the amount of precipitin remaining in solution in the presence of the precipitable substance is apparently a function of the concentration of the precipitable substance—crystalline egg albumin, the colloidal properties of which are indisputable. Although the experiment was not conducted upon a quantitative basis, the regularity of the graph of its results is striking. From this feature it is a fair assumption to suppose that the reacting antibodies were strictly homologous, and that the absence of irregularity in the curve is evidence that the antigen was a relatively simple substance. This confirms the chemical evidence of the purity of the preparation of crystalline egg albumin used as the antigen.

Summary.

In these studies several phases of the precipitin reactions were investigated by the use of purified proteins as antigens. These preparations were edestin from hempseed and crystalline ovalbumin from fresh eggs. The ovalbumin isolated by the method of Hopkins and Pinkus was apparently as pure as is obtainable by chemical means. This albumin, however, produced moderately severe anaphylactic reactions in animals immunized with ovoglobulin. Anaphylactic tests of the individuality of a protein cannot be any longer regarded as the criterion of the individuality of the substance as an antigen. Wells and Osborne have shown that proteins of considerable chemical difference may have a common antigenic group, which causes mutual anaphylactic reactions in animals sensitized to these proteins. In particular, as egg globulin is a mixture of proteins, one of which is undoubtedly egg albumin, anaphylaxis produced by injections of albumin into animals sensitized to the so-called "globulin" offers no evidence for or against the purity of the albumin. The character of the curves shown in Fig. 1 confirms the assumption based upon chemical data, that crystalline egg albumin is a single protein.

2. With edestin and crystalline egg albumin as antigens, phases in the precipitin reaction were found in which these substances and their specific precipitins could be demonstrated to be co-existent, but ununited in the same serum.

3. Where edestin or crystalline egg albumin is injected into a rabbit immunized thereto, the antigen may be found in the circulating blood during 48 hours after its injection, while at the same time the animal maintains a high titer of free precipitin in its blood.

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4. When the pure protein antigen is mixed in proper proportions with the serum of a specifically immunized rabbit, and the resulting precipitate removed by centrifugation, the supernatant fluid contains both antigen and antibody.

5. The serum drawn from a rabbit during the periods in which free antigen and antibody are co-existent in the circulation, undergoes slow spontaneous precipitation when kept in sterile tubes in the ice-box. The graph of this reaction is reproduced as Fig. 1. The relationship of this parabola indicates that the interaction of antigen and antibody takes place according to a definite law. When sufficient quantitative data are obtained to allow an analysis of this curve, the formula for this reaction will undoubtedly throw light upon the chemical or physical reaction of the process.

6. The protective action of the solution of egg albumin as a third colloid, preventing precipitation in a reaction between human serum and its antibody, was readily demonstrated. This observation, and the constancy of the long "prozone" in precipitin test with egg albumin are in accord with the protective action of ovalbumin upon colloidal gold.

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CARCINOMA OF THE PLEURA WITH HYPERTROPHIC OSTEOARTHROPATHY.

REPORT OF A CASE WITH A DESCRIPTION OF THE HISTOLOGY OF THE BONE LESION.

By STANHOPE BAYNE-JONES, M. D.

(From the Pathological Department, The Johns Hopkins University, Baltimore, Md.)

The patient, whose case provided the material for this report, presented the not uncommon association of chronic intra-thoracic disease with a peculiar form of chronic disease of the bones. The extreme degree of both of these processes made his case somewhat unusual. The change in the bones, which began after the onset of the thoracic disease and progressed with it, was typical of the condition known as "secondary hypertrophic osteoarthropathy." The nature of the intra-thoracic disease, however, remained obscure throughout the patient's illness. From the material obtained at autopsy, this was found to be an extensive pleural neoplasm, with a cellular picture characteristic of the so-called "primary carcinoma of the pleura." The account of the case, with emphasis upon the two main diseases, may be summarized as follows:

ABSTRACT OF MEDICAL HISTORY No. 102737.—J. H., a negro boy, 16 years old, was admitted May 22, 1915, to the Medical Clinic of The Johns Hopkins Hospital, complaining of "pain in the left side of the chest, weakness and shortness of breath." Until the onset of the symptoms which began three months before he came to the hospital, he had been an athletic school-boy. During these months he had several attacks of pain in the left side, associated with some fever and vomiting, and so much "pain around the heart," that he was confined to bed. He had remained in bed during the month previous to his admission, lying curved toward the left side. He had lost some weight and his ankles had become swollen.

When examined in the hospital, he was found to be an emaciated boy, lying on his left side. The important physical signs were shown by his chest and skeleton. The conspicuous skeletal change was a general enlargement of the long bones. The fingers and toes were club-shaped. The forearms were elongated disproportionately to the humerus and the distal ends of the radii and ulnæ were thickened. The clavicles were also thickened. The tibiæ were enlarged, especially their lower ends. The ankles and knees were slightly swollen, but were not painful and did not contain an excess of fluid. The spine was widely scoliotic, with the con-

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cavity to the left. These changes in the bony framework are shown in the accompanying photograph of the patient (Fig. 1). Roentgenograms of the

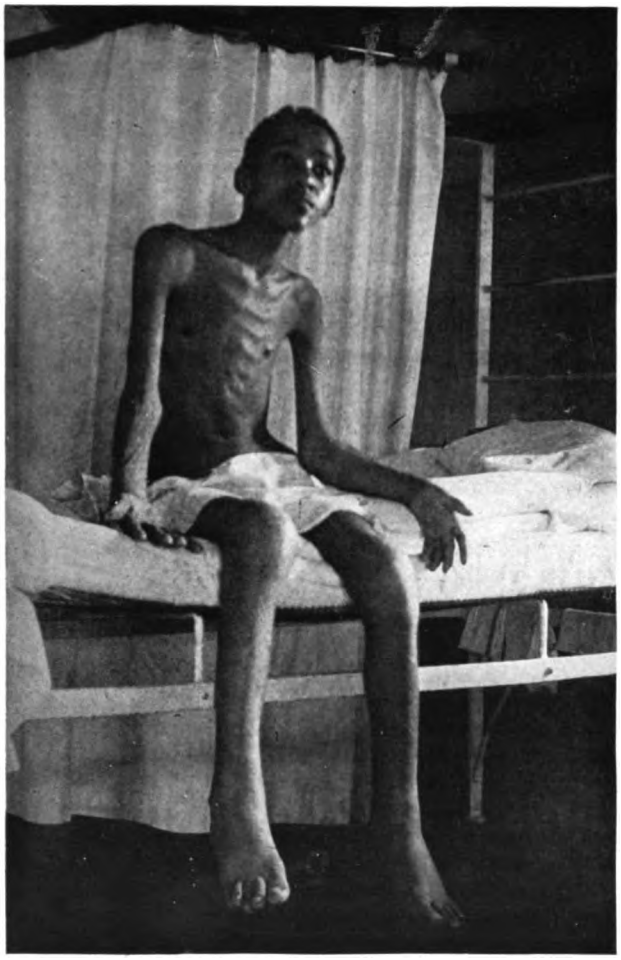

FIG. 1.—Photograph of patient showing the general features of hypertrophic osteoarthropathy, with a deformity of the thorax due to the pleural neoplasm. The enlargement of the long bones and the clubbing of the fingers and toes are plainly seen.

patient's arms, legs and hands were taken before the pulmonary condition was studied. In these plates (Figs. 2, 3) a fairly regular shadow was seen lying along the outside of the usual line cast by the cortex of the bone,

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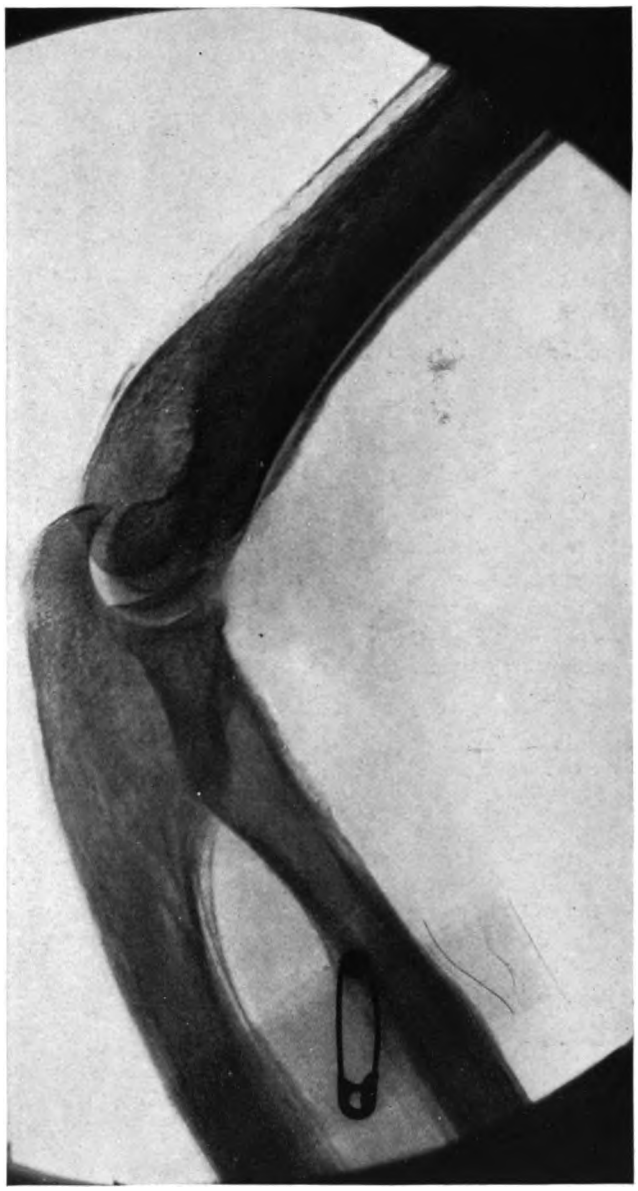

FIG. 2.—Roentgenogram of humerus, ulna and radius, showing the accessory shadow along the shafts of the bones, cast by the encasing layer of newly formed subperiosteal bone.

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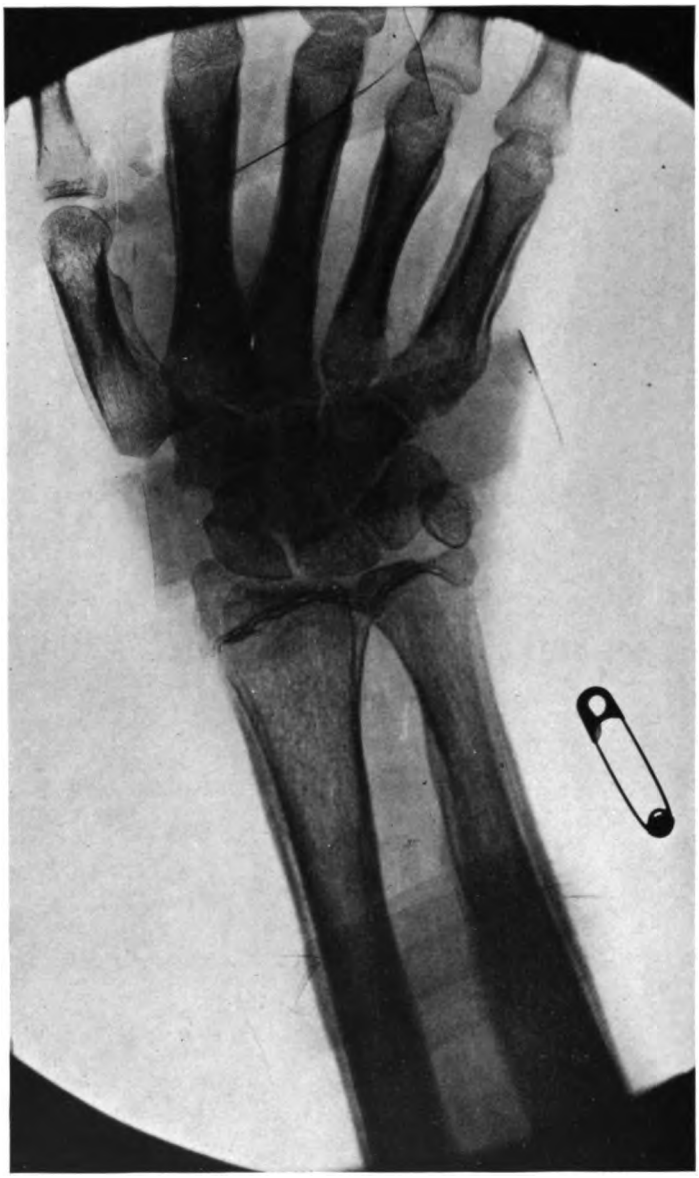

Fig. 3.—Roentgenogram of lower ends of ulna and radius and metacarpus. The third layer of new bone is shown by these shadows to involve also the metacarpal bones. The epiphyseal lines are normal.

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evidently representing a new formation of bone beneath the periosteum. The condition was at first diagnosed as a hypertrophic periostitis of syphilitic origin. The patient's Wassermann test was negative, and that of his father was also negative. From the circumstances of the case it seemed that syphilis could be definitely excluded.

The physical signs over the left chest, where the percussion note was flat and the voice sounds had a nasal quality, suggested the presence of an effusion or pus in the subscapular region. No fluid, however, was discoverable by thoracentesis at this time, or subsequently.

During the succeeding months, the patient continued to have an irregular fever, with a temperature varying between 99 and 101° F. Repeated punctures of the chest failed to reveal the nature of the process there. Pulmonary tuberculosis was suggested as a possibility, but this was apparently excluded by a negative Calmette eye-test with 5 per cent tuberculin. The patient's leucocyte count remained at about 10,000 to 12,000 cells per cu. mm., with 75 to 85 per cent polymorphonuclear neutrophiles. He failed steadily, receiving no benefit from any form of treatment. An exploratory thoracotomy was done on August 24. When a rib was resected, a layer of thick yellow tissue was found in place of the pleura, without any effusion in the chest. A frozen-section of this tissue was diagnosed "sarcoma of the pleura," and no further operation was attempted. Shortly after the operation, the patient began to have pains in the abdomen. He failed steadily and died one week later.

Abstract of Autopsy No. 4455.—*Anatomical Diagnosis.*—Primary: *Primary carcinoma of the pleura*, filling left pleural cavity, invading left lung, pericardium, diaphragm, capsules of liver, spleen and left kidney; implantations of carcinoma on intestines; acute hemorrhagic peritonitis; atelectasis of left lung; deformity of thorax; scoliosis.

Subsidiary: Pulmonary tuberculosis (encapsulated tubercles at right apex); chronic fibrous pleurisy (rt.).

Generalized hypertrophic osteoarthropathy.

The chief pathological changes were found in the thoracic organs, particularly the pleura, and in the bones. The description of these are quoted from the protocol as follows:

The *body* is that of a greatly emaciated young mulatto, 162 cm. in length. The orbital and other facial fossæ are deeply sunken and the bony skeleton stands out prominently. The thorax is deformed, being depressed and retracted on the left side; it is flattened in front and bulges to the right in the axilla on the right side. There is an extreme grade of scoliosis of the dorsal spine, with the convexity toward the right. In the back, below the angle of the left scapula, is an oval opening at the site of the surgical operation. A thin purulent fluid passes out along the drain inserted into this opening. By passing the finger into this opening, it is determined that parts of the 9th and 10th and 11th ribs have been removed. A short distance beyond the chest wall, the finger comes in contact with a firm, somewhat nodular structure, which extends throughout the part of the chest which can be explored with the finger. The *long bones* of the body are thickened

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and roughened and the joints of the hands, knees and feet seem to be diffusely enlarged. The ends of the fingers are somewhat club-shaped with the fingernails curved both transversely and longitudinally. There is a long scar above the ulna of the left forearm. Rigor mortis is present in all the joints.

The *abdomen* is flat, with thin, rigid walls, in which there is practically no adipose tissue. The peritoneal cavity contains about 40 c. c. of bloody fluid. The walls of the abdomen and the various viscera are splotched here and there with dark brown and yellowish areas. The largest of these areas is in the left dome of the diaphragm, where the tip of the spleen and the left lobe of the liver are adherent to a brown granular area of the diaphragmatic peritoneum. This area is composed chiefly of what seems to be a delicate granulation tissue together with small extravasations of blood in the sub-peritoneal tissue. Throughout this region also are numerous yellow specks, which are rather firm and seem to be in direct connection with the mass above the diaphragm. Portions of the intestional peritoneum show a similar change, especially over several loops of the small intestine which lie in the pelvis. Here, in addition to the hemorrhagic material, there are localized collections of yellow friable material—apparently a thick exudate. Two intussuceptions are present in the upper part of the small intestine; but these are readily separable and are not composed of inflamed intestine. The *left pleural cavity is obliterated by a large mass*, while on the right the lung is bound to the chest wall by dense adhesions, which obliterate this cavity. There is no free fluid or localization of pus in either pleural sac. The *thymus* extends down from the episternal notch; it is 6 cm. in length. The pericardial sac contains about 15 c. c. of slightly blood-tinged fluid. The *pericardium* is generally smooth, except for three areas on the left posterior side, where several types of lesions are visible. One of these is a small yellow nodule, 2 mm. in diameter, entirely sub-pericardial. (Fig. 5.) The other spots, of similar size, have a dark brown, granular surface, not unlike the patches seen in the peritoneum. On section it is seen that these nodules are in direct connection with the tumor in the left chest, which is in contact with the pericardium at this situation. The heart itself shows nothing abnormal.

Lungs.—The pleural covering of the right lung is thickened by fibrous tissue which binds the lung firmly to the chest wall. The lower and middle lobes of the right lung are crepitant, and have a pinkish-yellow moist surface on section. At the apex of the upper lobe, several firm nodules are palpable. On section, this area of the upper lobe contains several greyish areas, about 2 mm. in diameter, which stand out above the level of the section and are surrounded by small dark purple zones. The bronchial lymph nodes are pigmented, but the nodes at the hilum of this lung are apparently not enlarged. The pulmonary arteries and veins are not abnormal. The *left side of the chest is filled by a large tumor mass* (Fig. 4), which has its thickest area in the lower posterior portion of the chest and envelops the whole of the lung like a shell. The tissue composing this tumor mass is fairly firm, nodular and of a yellow color speckled with brown hemorrhagic

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areas. The tumor passes upward over the lung in flat sheets and by thin extensions into the interlobar and pleural complementary spaces. It is

FIG. 4—Photograph of carcinoma of the pleura enveloping the lung. The neoplasm is pinned back at the upper end of the mass to show the sheet-like type of growth.

intimately connected with most of the left side of the diaphragm, through which it seems to be extending in the region where the spleen and left lobe of the liver are adherent. Several processes seem to invade the peri-

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cardium, and in several places definite prolongations and nodular portions of the tumor can be traced into the lung substance.

The *left lung* is compressed within the enveloping tumor. The lung

FIG. 5.—View of the posterior aspect of the pericardium showing nodules of tumor where the carcinoma of the pleura has invaded this sac.

tissue is generally darker in color than that of the right lung and has a fleshy non-crepitant consistence. Except for the nodular masses of tissue resembling the tumor-tissue, there are no areas of consolidation of this

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lung. At the hilum, the lymph-nodes are involved in the tumor and are enlarged and nodular. The arteries and veins are not abnormal.

The *spleen* is adherent by its upper pole to the red, granular areas on the upper surface of the left diaphragm. Its capsule is thickened at these places of contact, and the section seems to show small strands of tissue, like that of the tumor passing into the spleen itself. The pulp does not come off on the knife and the Malpighian bodies appear as small grey dots, but are very numerous. The spleen measures 10.5 x 3.5 x 2 cm.

The *liver* weighs 700 gm. and measures 22 x 14 x 5 cm. The capsule is thin and delicate everywhere except for a small region over the upper part of the left lobe where it is adherent to the diaphragm and is apparently invaded by the growth from the thorax. The liver substance is light brown in color, showing distinct lobulation, with apparently the normal amount of connective tissue.

The *stomach*, *pancreas* and *adrenals* show nothing abnormal.

The *kidneys* together weigh 200 gm. Both present the same general appearance, except that the capsule of the left kidney in a small area near its upper pole does not strip as smoothly as the capsule over the rest of the organs. At this point the kidney lies in contact with a downward prolongation of tissue resembling the tissue of the tumor in the left chest, and it seems as if the renal cortex were invaded for a short distance by a small strand of this tissue.

Long Bones.—A portion of the ulna, taken from the region of the old operative scar in the left forearm, does not show any evidence of neoplasm. But this bone, the fibula, tibia and femur, on section show a layer of spongy bone lying below the periosteum outside the ring of dense normal bony cortex. In all these bones, three osseous layers are readily visible, *viz.*, a spongy medulla, a dense cortex, and a layer of spongy sub-periosteal bone. The original bone is rarefied. The epiphyseal lines are somewhat irregular.

The *thyroid* is definitely enlarged, weighing 60 gm. The lobes are equal in size; the left measures 6.5 x 3 x 2 cm. On section the surface has a translucent jelly-like appearance and is light red in color. A sticky material can be scraped from the surface, coming off in small granules which correspond to the alveolar spaces.

Microscopical Notes.—A section from the *tumor* shows an invasive proliferation of epithelial-like cells, constituting a neoplasm whose chief characteristic is the formation of alveolar and tubular structures separated from each other by connective-tissue stroma and filled with large epithelial-like cells. The cells are large, polygonal, with single and double vesicular nuclei. Relatively few mitotic figures are visible, but the cells tend to be packed together in nests showing many nuclei with little intercellular differentiation. Strands of these cells, of varying thickness, and single cells invade the surrounding stroma; there are areas of hyalinization of the connective tissue and numerous extravasations of blood (Figs. 6, 7).

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Sections showing metastases, implantations and invasions of the neoplasm in neighboring organs: In the section from the *lung*, strands and alveoli composed of the characteristic epithelial-like cells extend from the pleural surface into the lung tissue. Areas of hemorrhage surround these prolongations of the tumor.

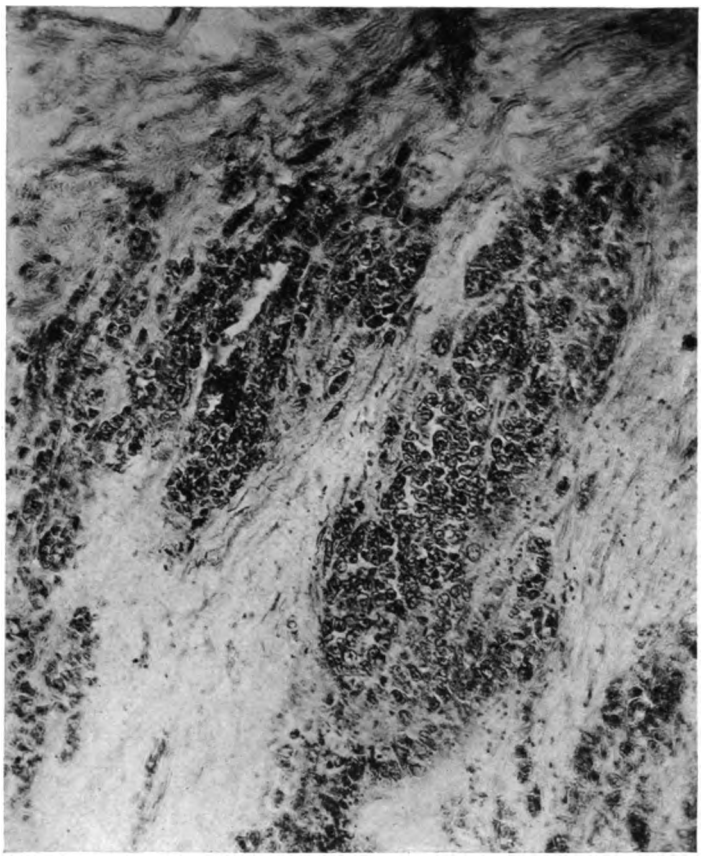

Fig. 6.—Section from carcinoma of the pleura showing the characteristic arrangement of the large cells in a stroma of hyalinized and hemorrhagic connective tissue.

The rest of the lung is so compressed that the alveolar spaces can be distinguished only indefinitely, and the bronchi are flattened.

The *pericardium* shows one or two nodules of these characteristic cells in the pericardial stroma, making a bulge on the cardiac surface. Throughout this section, there is a considerable amount of hemorrhage and hyalinization of the connective tissue.

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In the capsules of the *spleen* and *kidney* strands and alveoli of the neoplastic cells are abundantly present. They do not, however, invade the parenchyma of either of these organs.

On the under surface of the *diaphragm* there is a somewhat papillomatous formation of the extension of the tumor.

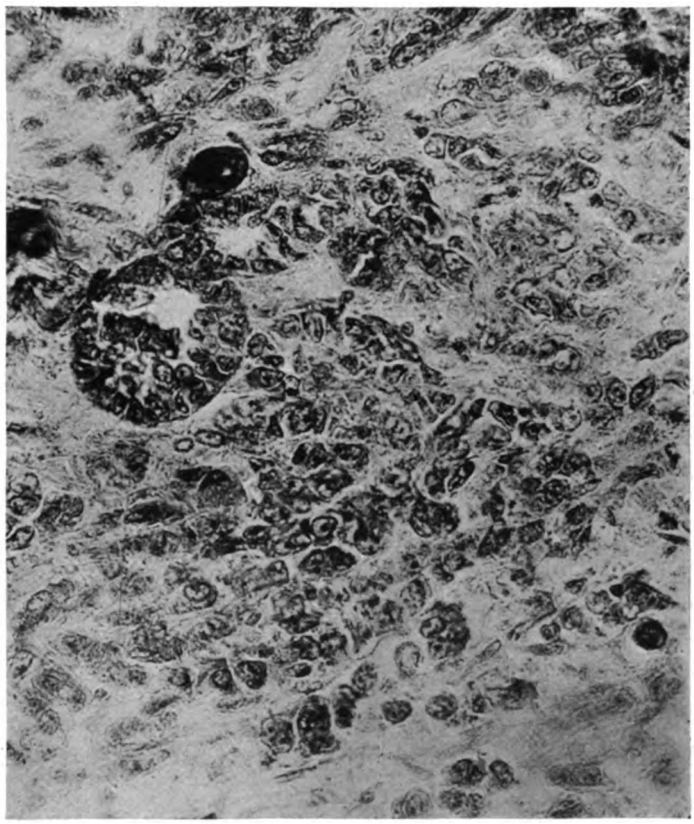

FIG. 7.—Section from carcinoma of the pleura under high power, showing the large epithelial-like cells, and the arrangement in a pseudoalveolus.

On the peritoneal surface of the *intestines* there are implantations of the characteristic tumor cells. These invade the connective tissue of the subserosa, and are surrounded by hemorrhage and hyalinized connective tissue. The muscular and mucous coats are not disturbed.

Lung.—In a section from the *right apex* there are several pink, granular areas, containing a few fragmented nuclei, and around this is a zone of round cells, epithelioid cells and capillaries. Beyond this, a zone of

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collapsed pulmonary alveoli grade into normal lung tissue. *Hilic lymph-node:* In this section are extensive hyalinized areas in the centers of the follicles and an occasional small but typical tubercle. Lymph-nodes from the cardiac end of the stomach and from the mesentery show nothing abnormal.

Thyroid.—The alveoli are large, distended with colloid and lined with very flat cuboidal epithelium. This section has distorted the tissue a good deal, but apparently shows a moderate degree of colloid goitre.

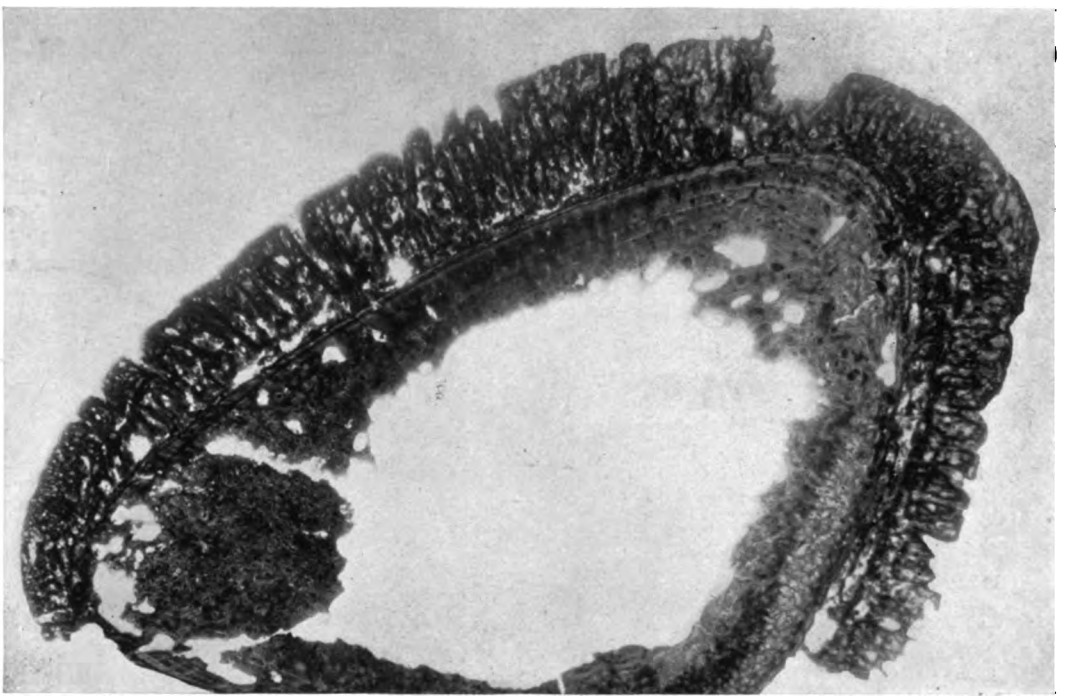

FIG. 8.—Photograph of cross-section of ulna, showing the layer of subperiosteal new-formation of bone, deposited in lines perpendicular to the circumferential lamellæ of the original cortex.

Bones.—Sections from the *tibia* and *fibula* show three distinct layers of bone in each of these places. (Fig. 8.) The inner layer consists of the usual wide-meshed cancellous tissue of the marrow cavity. The middle layer, corresponding to the cortex of normal bone, is composed of compact bone, arranged in lamellæ and with Haversian systems. The Haversian canals are enlarged and the cross-section of the cortex is thinned, indicating some rarefaction. Between this original cortex and the outer layer of bone in these sections there is an open meshwork of osseous trabeculæ merging shortly into the third layer of compact bone. This accessory

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layer of bone is composed of Haversian systems deposited in radiating lines which are perpendicular to the external circumferential lamellæ of the original cortex. In this new tissue, the lacunæ, canaliculi and lamellæ have all the characteristics of normal bone. The periosteum is seen lining the outer layer of new bone.

The bone-marrow is composed chiefly of fat cells, delicate fibrous tissue and numerous small blood-vessels.

The epiphyseal line of the lower and of the fibula consists of a thin broken zone of cartilage, partially calcified.

The articular cartilages of the knee-joint are smooth and are not obviously thinned.

Discussion.

As the chief features of this case were concurrent, they will be discussed separately, the disease of the pleura being considered first, and secondly the disease of the bones.

Carcinoma of the Pleura.—Among the neoplasms of the pleura, the growth known as "primary carcinoma" is probably the least frequent. Hansemann [1] found one primary tumor of the pleura in 1200 autopsies. Lord [2] accepted 50 cases from the literature up to 1915. Among the 5000 autopsies performed in this department, two were upon cases of primary carcinoma of the pleura (Sprunt [3]).

The first case of pleural carcinoma was described by Wagner [4] in 1870, under the name of "Das tuberkelähnliche Lymphadenom." The cancerous nature of the growth was recognized in 1876 by Schultz,[5] who called it "endothelial carcinoma." By other authors, as shown in a recent review by Rosenbaum,[6] it has been termed "endothelioma," "endothelioma lymphangiomatosum," "pleuritis carcinosa," "lymphangitis carcinomatodes," "lymphangitis prolifera," and "sarcocarcinoma." This confusing terminology indicates that in the minds of the describers of the tumor there have been two uncertainties. These questions were: (1) What is the origin of the tumor? From the lining cells of the pleura or from the intima of the lymphatics? (2) What is the nature of the cells lining the pleura?

The obscurity around the origin of the tumor has been due to the fact that in most cases the growth has been too far advanced, involving the whole pleura, to show its origin. In spite of the fact that the large polygonal cells composing the tumor have little in common with the endothelium of lymphatics, many authors have decided that the neoplasm grew from these structures. Two observers, however, were able to oppose definite evidence to this hypothesis. Benda [7] and Sprunt [3] found areas in their sections in which transitions from the flat cells

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of the pleural lining to the villous and tubular arrangements of the large cells of the tumor could be seen. These observations indicate that the neoplasm arises from the lining cells of the pleura.

At present, most histologists regard the lining cells of the pleura as epithelial-like cells derived from the mesoderm. It is certain that these cells do not arise from endoderm, but from the cells of the mesoderm, when this layer splits to form the pleural cavity. These cells have many of the characteristics of epithelium, and are commonly designated "mesothelial epithelium." It is appropriate, therefore, to regard this primary neoplasm of the lining cells of the pleura as an epithelial tumor—a carcinoma of the pleura.

In most cases, as in this one, vascular metastases are uncommon. The neoplasm invades the lung, pericardium and diaphragm, making secondary growths by direct extension, and forming implantation metastases upon the surfaces of the organs lying in cavities into which the tumor has penetrated. The envelopment of the lung, and sheet-like extension of the growth throughout the whole of one side of the thorax is a distinguishing characteristic of this type of pleural neoplasm.

Secondary Hypertrophic Osteoarthropathy.—In this discussion, it has been emphasized that the association of hypertrophic bone changes with chronic disease of the lung is an accidental, although frequent occurrence. The disease was first described by Marie,[8] in 1890, as "osteoarthropathie hypertrophante pneumique," and since then it has been frequently called "pulmonary osteoarthropathy." The present simplified terminology is adopted from the designation used by Locke,[9] who showed that this type of hypertrophic sub-periosteal bone formation has been associated with a great variety of diseases. From his studies of the literature he was able to group the cases according to the primary disease, as follows: With all types of chronic disease of the respiratory tract (including carcinoma of the pleura), 108 cases of hypertrophic osteoarthropathy; with diseases of the circulatory tract, 6 cases; with disease of the alimentary tract, 13 cases; with miscellaneous conditions, chiefly chronic suppuration, 7 cases. In all the reports of the disease, Locke found only six cases which suggested the possibility that the bone changes were primary. He concluded, therefore, that the "evidence is overwhelming that hypertrophic osteoarthritis is always a secondary disease."

The secondary nature of the disease, however, does not throw any light on its etiology. It is usually secondary to chronic tuberculosis,

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and often secondary to chronic suppuration. On this basis it has been supposed that some toxic product in these lesions stimulates the periosteum to the formation of a new deposit of bone. On the other hand, generalized hypertrophic osteoarthritis has been associated with so many varied non-suppurative diseases, that the toxogenic hypothesis of its origin is insufficient. The few experiments undertaken to reproduce the condition are too inconclusive to be of any value, and the case reported in this paper does not afford any data for an interpretation of the etiology of the bone changes.

The complete review of the subject published by Locke[9] in 1915 renders superfluous any detailed discussion of this disease. The case reported here, however, has several interesting features which may be pointed out as follows:

1. The hypertrophic bone changes consist of a regularly arranged deposit of new bone in a layer around all the bones of the skeleton. This layer is approximately of the same tickness on all the bones of the arms and legs.

2. The periosteum is found to be on the outer edge of the most recently formed bone, which apparently indicates its active participation in the process.

3. The histology of the newly formed bone shows that this tissue resembles normal bone in all respects and that, while it does not show any evidence of inflammation, it is similar to the new bone formed in cases of definite periostitis.

4. The hypertrophic osteoarthropathy was obviously secondary to the primary carcinoma of the pleura, and progressed with that disease.

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THE INTERRELATION OF THE SURVIVING HEART AND PANCREAS OF THE DOG IN SUGAR METABOLISM.*

By ADMONT H. CLARK, M. D.

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The problem of sugar metabolism and diabetes is intimately associated with the two following questions: (1) Does the pancreas have a local independent action on dextrose passing through its blood-vessels, altering the dextrose in some way for utilization by the body tissues? (2) Is there a direct interrelation between the pancreas and body tissues in dextrose metabolism, and if so, how is it accomplished?

In the experimental work reported below, the attempt has been made to gain some evidence as to the first of these questions by the direct perfusion of the pancreas with physiological concentrations of dextrose. The second question has been studied by various types of perfusion experiments on the isolated surviving heart and pancreas in order to determine whether there was any interdependence between the two in dextrose metabolism.

The numerous experiments recorded by various workers bearing upon the interrelation between the pancreas and body tissues in the utilization of dextrose need not be reviewed in detail. It is sufficient to say that two general lines of investigation have developed. On the one hand, the experiments of Hédon,[1] Carlson and Ginsburg,[2] Forschbach,[3] Carlson and Drennan,[4] Verzár and von Fejér,[5] Woodyatt,[6] Murlin and Kramer,[7] and others, in which blood was transferred in various ways from normal to diabetic animals in the hope of thus supplying a pancreatic hormone, have yielded no decisive results. Again, Verzár and von Fejér,[5] Murlin and Kramer,[7] Scott,[8] and others have attempted to supply this hypothetical internal secretion by the injection into diabetic animals of various kinds of pancreatic extracts. Their results have in general been negative. The obvious objection can be raised to all such experiments that in grinding the pancreas its powerful proteolytic enzymes might readily inactivate a more delicate product of internal secretion.

The second main line of investigation has developed since Cohnheim[9] in 1903 reported experiments in which he found that, while pancreatic extract

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TABLE I.

SUMMARY OF EXPERIMENTS ON THE UTILIZATION OF DEXTROSE BY THE ISOLATED MAMMALIAN HEART.

Author.	Date.	Type of heart.	No. of experiments.	Circulating medium.	Strength of dextrose perfused.	No. of hrs. perfused.	Interval between sugar determinations.	Dextrose disappeared per gm. of heart per hr.	Bacterial counts.	Final perfusate hydrolysed.	Aseptic precautions. Special notes.
					Per cent			*mg.*			
J. Müller.[17]	1904	Cat.....	4	Ringer-Locke's.	0.1±	2–6	At end of experiment.	2±	None.	No.	Not mentioned. Heart estimated as 12 gm.
Locke and Rosenheim.[18]	1907	Rabbit...	4 beating. 3 not beating.	Ringer-Locke's.	.0.1–0.25	7–10	At beginning and end of experiment.	11.2–1.7	None.	Yes.	Not mentioned.
Camis [19]....	1908	Rabbit... Cat.....	20 9	Ringer-Locke's.	0.1±	25–60 min.	At end of experiment.	0 13	None.	No.	Not mentioned. Cat's heart estimated as 12 gm. Rabbit's heart estimated as 8 gm.
Rohde [20]....	1910	Cat.....	12	Ringer-Locke's.	0.2	4±	At 2d and 4th hrs.	0.98 1st. 1.64 2d.	None.	No.	Apparatus washed with alcohol. Aseptic surgical technique not mentioned.
Gayda [21]....	1912	Rabbit...	10	Ringer-Locke's.	0.1	4–6	At end of experiment.	3.8–14.9 Av. 7.1	None.	No.	Apparatus washed with alcohol. Aseptic surgical technique not mentioned.
Knowlton and Starling.[22]	1912	Dog.....	10 normal. 7 diabetic.	Heart-lung preparation.	0.2–0.89	1–3	1 hr. ±.....	Normal 4 Diabetic 0	None.	No.	Attempt at sterilization of apparatus in a few experiments. Aseptic surgical technique not mentioned.
Neukirch and Rona.[23]	1912	Cat.....	Glucose 1.	Ringer-Locke's.	1.0	6½	At end of experiment.	1.6	None.	No.	Apparatus sterilized with concentrated acid and water. Aseptic surgical technique not mentioned.

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Maclean and Smedley.[24]	1913	Rabbit... Dog.....	4 3	Ringer-Locke's.	0.1–0.2	1–4	Successive hrs.	0.7 (av.) 1.3 (av.)	None.	No.	Apparatus sterilized in autoclave. "Ordinary aseptic precautions."
Maclean and Smedley.[25]	1913	Diabetic dog.	12	Ringer-Locke's.	0.1–0.3	3	.....	0+	None.	No.	Apparatus sterilized in autoclave. "Ordinary aseptic precautions."
Mansfeld.[26]	1913	Rabbit...	5 normal. 8 fever.	Ringer-Locke's.	0.1	3	At 1½ and 3 hrs.	Normal 2.2 Fever 4.4	None.	No.	Not mentioned.
Patterson and Starling.[27]	1913	Dog.....	9 normal. 14 diabetic.	Heart-lung preparation.	0.2–0.7	1–3 2	At end of experiment.	Normal 0+ Diabetic 0+	None.	No.	Apparatus washed with soda and occasionally boiled. Aseptic surgical technique not mentioned.
Cruickshank.[28]	1913	Dog.....	6 normal. 13 diabetic.	Heart-lung preparation.	0.4–0.6	1–4 1½–4	.....	.....	None.	.....	Same as preceding experiment. Experiments conducted to study glycogen content of hearts.
Cruickshank and Patterson.[29]	1913	Cat..... Dog.....	14 8 diabetic.	Ringer-Locke's.	0.2–0.3	1–3	Perfusions divided into two periods.	1.5 0.9	None.	Yes.	Apparatus washed with boiling water. Aseptic surgical technique not mentioned.
Starling and Evans.[30]	1914	Dog.....	Numerous.	Heart-lung preparation.	?	Varying.	.....	Estimated from RQ. 1.6	None.	No.	Not mentioned.
Underhill and Prince.[31]	1914	Rabbit...	25	Ringer-Locke's.	0.1	2	At end of experiment.	0.7–3.8	None.	No.	Apparatus sterilized in autoclave. State that aseptic precautions were observed.

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or muscle extract alone had no effect on dextrose, a mixture of the two caused a rapid disappearance of sugar, which he interpreted as being due to an oxidative process. Although his results were attacked by Claus and Embden [10] and others, they were supported by Arnheim and Rosenbaum,[11] Dewitt,[12] and Hall,[13] and were generally accepted until Levene and Meyer [14] in 1911 found that this apparent destruction of dextrose was due to a condensation process, for by hydrolysis the reducing sugar was restored.

Method.

The method of isolated perfusion was chosen in the following experiments, for, while obviously artificial compared with normal physiological conditions, it offered a method of controlling the factors concerned.

Two references only to the direct perfusion of the pancreas have been found. Hustin [15] perfused the pancreas in a study of its external secretion, and de Meyer [16] in 1910 found that by adding a solution previously perfused through a pancreas to one subsequently perfused through a liver there was an increase in the liver glycogen. The findings of fifteen observers who have studied the utilization of sugar by the isolated mammalian heart are summarized in Table I. An analysis of their results brings out the following criticisms:

1. A uniform type of animal has not been used.
2. The conclusions of the different observers are based on no constant time period of perfusion, but vary from 25 minutes to 10 hours.
3. Save for the experiments of Maclean and Smedley,[24] there has been no attempt to make hourly sugar determinations in order to follow the rate of sugar disappearance.
4. There has been a great discrepancy between the findings of various workers as to the amount of dextrose used by the living heart. Patterson and Starling [27] in the most recent work, using a heart-lung preparation and correcting for the sugar destroyed in the lung, found very little if any sugar used either by a normal or diabetic heart in periods of 1 to 3 hours.
5. Locke and Rosenheim [28] and Cruickshank and Patterson [29] are the only workers who hydrolyzed the final perfusates to determine whether by so doing there was an increase in the reducing substance present.
6. The observance of aseptic precautions has varied greatly with different workers. Maclean and Smedley [25] and Underhill and Prince [21] alone state that their apparatus was sterilized in an autoclave. In no instance save in the experiments of Underhill and Prince is there mention of scrupulous, aseptic surgical technique, and in no instance are bacterial counts given.

The importance of this last criticism has been emphasized by the results of this investigation. Infection of the perfusing liquid occurs easily, and its occurrence may account for a slight or even a considerable disappearance of dextrose. Extreme care in sterilization of the

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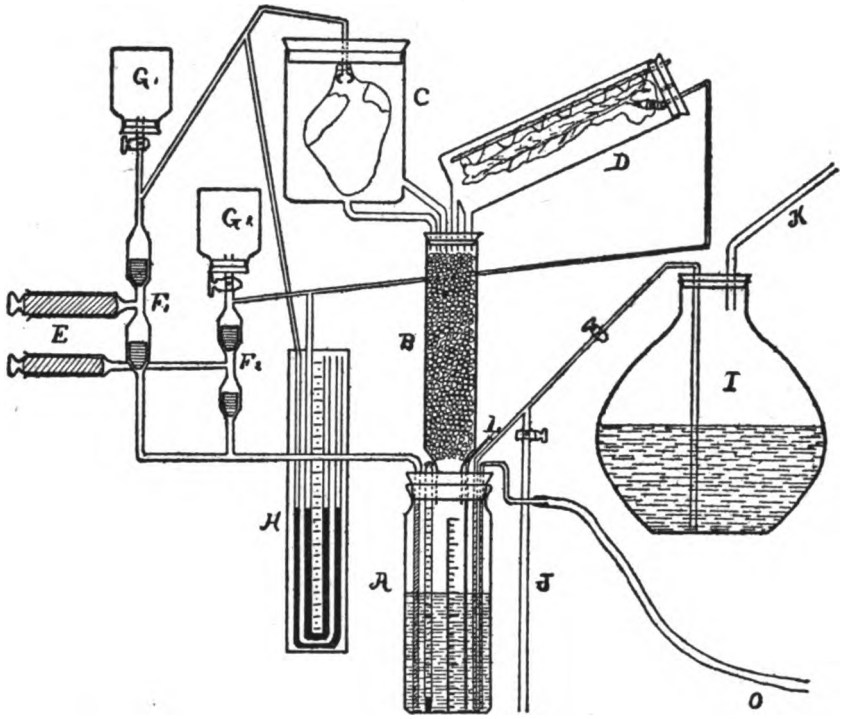

FIG. 1.—Diagram of the perfusion apparatus. Reduced to about one-sixth.

A. Reservoir containing the perfusion fluid, consisting of a 400 c. c. graduated glass bottle with a rubber stopper through which the various tubes and thermometer pass.

B. Artificial lung consisting of a glass cylinder filled with glass beads.

C. Glass perfusion chamber in which the heart is suspended from the bulb-shaped cannula tied in the aorta. The cannula passes through the large rubber cork. The fluid after perfusing through the coronary arteries flows from the auricles and passes down through the lung into the reservoir.

D. Glass perfusion chamber in which the pancreas is suspended by its mesenteric border to the long glass arm which projects from the rubber cork. The cork is perforated by an opening for the escape of oxygen and one for transmitting the cannula to the pancreatic artery. The perfused fluid drips from the pancreas and flows down through the lung to the reservoir.

E. 3 and 5 c. c. Luer syringes acting as pumps, and operated by a motor attachment.

F_1 and F_2. Glass two-way valves.

G_1 and G_2. Glass bottles acting as air-heads.

H. Double manometer connected with each of the delivery systems.

I. Reserve reservoir with siphon connection to the perfusion reservoir.

J. Tube for draining the perfusion reservoir.

K. Blow-tube for starting the siphon.

L. Small tube for removing samples of perfusate for analysis.

O. Oxygen tube. The oxygen bubbles through the reservoir and passes up through the column of beads against the stream of perfusate coming down from the organs.

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apparatus and the observance of strict aseptic precautions are necessary to exclude this factor. All my final experiments were controlled by bacterial counts, and those in which the precautions against infection were not successful, as shown by the bacterial counts, were discarded. It seems evident that previous workers have failed to realize that not only must ordinary aseptic precautions be used, but that only by the minute observance of the most rigid care controlled by bacterial counts can bacteria be sufficiently excluded to make the conclusions as to sugar utilization in such experiments reliable.

Apparatus.—The diagram of the apparatus used is shown and explained in Fig. 1. Extreme care was taken to wash all adherent fat and protein from the apparatus immediately at the end of each experiment. Sterilization was accomplished by fractional sterilizaation in an Arnold sterilizer. Immediately before each experiment the apparatus was tested by perfusing several times with sterile Locke's solution, containing the percentage of dextrose to be used in the experiment. This technique was time-consuming, but was justified by repeatedly getting an apparatus, washings from which showed no bacteria on agar plates. The temperature of the apparatus and perfusate in all experiments was maintained at 37-38.5° C. by keeping the apparatus in a thermostat.

Perfusate.—The solution used in all experiments was a standard Ringer-Locke's solution of the following formula: Calcium chloride 0.024 per cent, potassium chloride 0.042 per cent, sodium bicarbonate 0.03 per cent, sodium chloride 0.9 per cent, dextrose (Kahlbaum's pure) 0-0.5 per cent (according to the experiment). Locke's solution was made up immediately before each experiment from freshly distilled water which was sterilized by boiling. The amount of perfusate was generally 250 c. c. and was left unchanged during the period of perfusion, save for samples removed for analysis.

Dextrose Determinations.—A slight modification of the colorimetric method of blood sugar determination described by Lewis and Benedict [7] was used. The great advantage which the method offered was that the small amount of fluid necessary for analysis did not materially diminish the volume of the perfusate, so that hourly observations were possible. The results reported in these experiments obviously depend on the accuracy of the technique of sugar determination. For this reason in the earlier experiments hourly duplicate determinations were made not only on the perfusate but on the control

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perfusion and on the original Locke's solution. The average error of duplicate determinations practically never exceeded 0.5 per cent of the total sugar present. Correction was always made for the amount of perfusate removed for analysis in estimating the total volume of sugar present in the perfusate.

Controls.—A small apparatus similar in all respects to the main apparatus, save that it contained no living tissue, was used in the first 47 experiments. Its reservoir of 50 c. c. was filled from the main apparatus after the heart or pancreas or both had been perfused for 10 minutes. Thus the control apparatus contained a fluid which was inoculated with whatever bacteria were contained in the main perfusate and with whatever enzymes were washed out in that time. In no experiment considered was there any change in the reducing properties of the sugar in the control perfusion beyond the limits of experimental error.

Bacterial Counts.—The plate method of bacterial counting was used throughout. Contaminating organisms were usually of the intestinal types. Although contamination generally occurred even with the most rigid precautions, it was possible to estimate from the number of bacteria present whether they were sufficient to account for a disappearance of sugar. Six experiments were obtained in which the liquid remained entirely sterile for the four-hour period of perfusion. Those experiments were discarded in which bacterial contamination might in any way be interpreted as having accounted for dextrose utilization.

Hydrolysis.—The method of hydrolysis used by Levene and Meyer [14] was followed: hydrolyzing for two hours with 1 per cent hydrochloric acid with a reflux condenser, and subsequently carefully neutralizing and bringing to the original volume. It was found that this percentage of acid gave the maximal hydrolytic effect. If a polymerization of the dextrose into some more complex, non-reducing form occurred, hydrolysis should restore it to the simple mono-saccharide. In this way it is possible to determine whether the disappearance of dextrose is a real utilization or only an apparent one.

Surgical Procedure.—Small or medium-sized dogs were used which had been previously fed on a routine meat-bread diet. Great care was observed in shaving and sterilizing the chest and abdomen of each dog. All instruments were sterilized by boiling. Rubber gloves and sterile gowns were worn by the operator and his assistant. The table

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and animal, except the narrow field of operation, were covered with sterile towels. In a word, every precaution of a major surgical operation was used. The dogs were anesthetized with ether.

Removal of the Pancreas.—The removal and perfusion of the pancreas is a simple operation. The abdomen was opened by a transverse incision just below the costal margin. The aorta was clamped as it emerged from the diaphragm, thus making the subsequent steps practically bloodless. The pancreaticoduodenal artery was exposed and a cannula placed in it. All the pancreas except the splenic portion, which is not supplied by the pancreaticoduodenal artery, was then gently removed. The common bile-duct must not be cut. The pancreas was then washed in warm sterile Locke's solution and loosely suspended by a continuous suture through its mesenteric border to the supporting arm of the perfusion chamber, and placed in the apparatus, as shown in Fig. 1. The cannula was connected and the perfusion started. The procedure can be carried out in less than five minutes. A pulsatile pressure whose systolic pressure never exceeded 40 mm. of mercury was used, and about 20 c. c. of fluid were perfused per minute. Carmine gelatin injections of the pancreas by this method showed that there was complete penetration of the fluid to every portion of the pancreas.

Removal of the Heart.—The technique of removal and perfusion of the heart scarcely need be described, as it was similar to that used by previous workers. The thorax was rapidly opened, the heart removed and transferred to a dish of warm sterile Locke's solution, where, after washing it free of any excess of blood, the cannula was tied into the aorta above the aortic valves. Care must be used to exclude air bubbles. The heart was placed in the perfusion chamber and perfusion begun at once. This procedure requires about three minutes. The heart generally beats vigorously from the first. At the end of four hours the heart always showed a varying amount of edema and dilatation. As soon as the hearts were allowed to die, however, and rigor mortis set in, a considerable amount of this fluid seemed to be squeezed out. In addition, every heart was mechanically squeezed free of as much fluid as possible. From gross appearance, the heart approximated its original size. The error that resulted from this procedure must have been slight and fairly uniform for all the experiments. In the last 13 experiments the hearts were weighed before and after perfusion, and the results justified the previous method.

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The amount of fluid perfused through the hearts varied from 20 to 60 c. c. per minute, according to the size of the heart. To force this amount of fluid through the coronary arteries required a pulsating pressure whose systolic pressure varied from 40 to 160 mm. of mercury, and the diastolic pressure from 20 to 100 mm. What factor caused this variation in the resistance of the coronary arteries has not been determined. In all experiments recorded, unless otherwise noted, the hearts continued to beat for the four-hour period.

Perfusion of the Heart and Pancreas.—In a simultaneous perfusion of the heart and pancreas from the same animal, the heart was first removed and then the pancreas, as described above. The double perfusion is shown in Fig. 1. It is obvious that the intimate mixture of the fluids passing through the two organs was practically equivalent to a perfusion of the organs in series. If the pancreas was to be perfused first, it was removed and the dog was kept under light ether anesthesia until the heart was required.

Results.

Pancreas Perfusions.—Eleven experiments were carried out before the technique of perfusion was perfected. In these experiments there was a distinct disappearance of dextrose from solutions perfused through the pancreas. This might have been interpreted as a utilization of, or change in, the dextrose, had bacterial counts not been made. Table II is given to illustrate these experiments, and shows that at the

TABLE II.

Infected Pancreatic Perfusion.

Fluid.	Sugar, 5 min.	Sugar, 3 hrs.	Sugar, 6 hrs.	Bacteria per c. c. at end of 5 min.	Bacteria per c. c. at end of 6 hrs.
	per cent	*per cent*	*per cent*		
Original Locke's solution.	0.3041	0.3030	0.3035	0	0
Control perfusion.....	0.3041	0.3058	0.3041	350,000	19,400,000
Pancreatic perfusion....	0.3026	0.300	0.2347	350,000	50,500,000

end of five minutes the perfusate contained about 350,000 bacteria per cubic centimeter. In the first three hours there was a slight drop in the precentage of dextrose. In the subsequent three hours there was a considerable loss of sugar but the bacterial counts at the end of this

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six-hour perfusion showed over 50,000,000 bacteria per cubic centimeter. With perfection of the technique, however, three successive perfusions of the pancreas were obtained in which the maximal bacterial count was 1,670,000. In none of these experiments was there the least detectable loss of dextrose. Table III shows the summarized results of these experiments. In them it seems evident that when

TABLE III.

PANCREAS PERFUSION.

Experiment No.	5 min.		1 hr.		2 hrs.		3 hrs.	
	Dextrose in perfusate.	Dextrose in control.	Dextrose in perfusate.	Dextrose in control.	Dextrose in perfusate.	Dextrose in control.	Dextrose in perfusate.	Dextrose in control.
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
22.....	0.298	0.298	0.300	0.299	0.298	0.299	0.300	0.300
23.....	0.601	0.601	0.599	0.597	0.601	0.600	0.599	0.601
24.....	0.10	0.10	0.099	0.099	0.100	0.099	0.10	0.10

Experiment No.	4 hrs.		5 hrs.		6 hrs.		Bacteria.		Dextrose after hydrolysis.	Dextrose disappeared per gm. of pancreas.
	Dextrose in perfusate.	Dextrose in control.	Dextrose in perfusate.	Dextrose in control.	Dextrose in perfusate.	Dextrose in control.	5 min.	6 hrs.		
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*			*per cent*	
22.....	0.298	0.299	0.298	0.299	0.300	0.300	40	22,560	0.296	0
23.....	0.600	0.600	0.600	0.600	0.601	0.599	12	295,000	0.599	0
24.....	0.099	0.10	0.099	0.099	0.099	0.10	101	1,670,000	0.099	0

dextrose is perfused through the pancreas there is neither a change of the dextrose into a non-reducing form, nor does hydrolysis alter its reducing properties.

Heart Perfusions.—In view of the variations reported by different workers as to the amount of dextrose utilized by the surviving heart, and in view of the obvious criticisms stated above, it was felt that before proceeding to perfuse the heart and pancreas together, it would be necessary to determine the utilization of dextrose by the heart alone under the conditions used in these experiments. Five successful

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TABLE IV.

CONDENSED TABLE OF EXPERIMENTS IN WHICH THE HEART WAS PERFUSED ALONE.

Experiment No.	Weight of heart.	Dextrose after 10 min. perfusion.	1st hr.			2d hr.			3d hr.			4th hr.			Dextrose per gm. of heart recovered by hydrolysis.	Average error of duplicate determinations.	Dextrose disappeared from control perfusion.
			Dextrose.	Dextrose diastase pared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose diastase pared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose diastase pared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose diastase pared per gm. of heart.	Bacteria per c. c.			
	gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*	*per cent*	
26....	84	0.200	0.201	0	85	0.199	0.03	83	0.200	0	1,888	0.192	0.237	3,500	0	0.66	0
27....	65	0.300	0.299	0.011	608	0.299	0	9,920	0.299	0		0.273	0.91		0	0.25	0
28....	46	0.368	0.368	0.018	190	0.367	0.036	258	0.366	0.043	53,200	0.3655	0.025	216,000	0	0.12	0
29....	69	0.501	0.497	0.11	44	0.499	0	7,100	0.473	0.933	7,800	0.456	0.678		0	0.65	0
34....	82	0.099	0.100	0	97	0.099	0	288	0.091	0.237	7,600	0.083	0.226	57,200	0	0.2	0

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TABLE V.

CONDENSED TABLE OF EXPERIMENTS IN WHICH THE HEART AND PANCREAS WERE PERFUSED TOGETHER SIMULTANEOUSLY.

Experiment No.	Weight of heart.	Dextrose after 10 min. perfusion.	1st hour.			2d hour.			3d hour.			4th hour.			Dextrose recovered by hydrolysis.	Average error of duplicate determinations.	Dextrose disappeared from control perfusion.
			Dextrose.	Dextrose clamped per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose clamped per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose clamped per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose clamped per gm. of heart.	Bacteria per c. c.			
	gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*	*per cent*	
30.....	97	0.196	0.179	0.465		0.167	0.306	12,200	0.143	0.60	23,600	0.126	0.42	50,400	0.49	0.49	0
31.....	128	0.399	0.333	1.28	50,000	0.286	0.92	200,000	0.273	0.212	500,000	0.272	0.042	800,000	0.27	0.5	0
32.....	128	0.300	0.272	0.531	49,600	0.231	0.756	512,000	2½ hrs. 0.213	0.34					0.031	0.4	0
33.....	102	0.100	0.077	0.557	960	0.058	0.45	16,700	0.041	0.395	108,460	0.025	0.384	356,000	0.19	0.32	0
37.....	86	0.100	0.089	0.30	1	0.054	0.964	1	0.035	0.532	2	0.026	0.245	2	0.54	0.32	0
39.....	98	0.200	0.165	0.872	1	0.142	0.57	0	0.128	0.356	4	0.123	0.113	26	0.47	0.34	0

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perfusions of the heart were obtained over a period of four hours, in which the maximal bacterial count was 216,000 per cubic centimeter. Table IV is a condensed chart of these experiments, and they are shown in an average curve in Fig. 2. The experiments indicate that during the first hour, in averaging the five experiments, the sugar utilization was 0.028 mg. per gm. of heart, in the second hour 0.013 mg., in the third hour 0.242 mg., and in the fourth 0.415 mg. It was felt that this disappearance of sugar in the last two hours was not due to bacterial action, for not only was there no loss of dextrose from the control perfusions, but in the perfusions of the pancreas for periods of six hours, in which the maximal bacterial count exceeded any of those in the heart perfusions, there was no loss of dextrose. In these experiments when the final perfusate was hydrolyzed there was no definite increase in reducing substance.

Heart-Pancreas Perfusions.—Six experiments were obtained in which the heart and pancreas were simultaneously perfused with the same fluid and in which the maximal bacterial count at the end of four hours was about 800,000 per cubic centimeter. In two of these experiments, as will be seen by consulting Table V, the perfusing liquid remained practically sterile throughout. In Experiment 32, the heart suddenly stopped at the end of about two and one-half hours. The figures, however, are given. The results are diagrammatically shown in Fig. 2 and summarized in Table VI.

TABLE VI.

TABLE COMBINING THE RESULTS GIVEN IN TABLES III, IV, AND V.

	1st hour.	2d hour.	3d hour.	4th hour.	Recovered by hydrolysis.
	mg.	*mg.*	*mg.*	*mg.*	*mg.*
Average utilization of dextrose per gm. of pancreas in 3 perfusions.	0	0	0	0	0
Average utilization of dextrose per gm. of heart in 5 perfusions	0.028	0.013	0.242	0.415	0
Average utilization of dextrose per gm. of heart in 6 heart-pancreas perfusions.	0.667	0.661	0.406	0.200	0.332

As the experiments progressed it became apparent, as shown in Fig. 2, that a striking phenomenon was occurring. The disappearance

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of sugar began in the first hour and was greatly in excess of that occurring when the heart was perfused alone. In the heart perfusions the distinct disappearance of sugar begins late, after the second hour of perfusion, but from this point on, during the period of observation, it occurs in an increasing ratio. When the heart and pancreas are perfused together, a striking loss of sugar occurs in the first hour, and towards the latter half of the experimental period of four hours this disappearance of sugar shows a decreasing ratio. Fig. 2 illustrates this point. The further fact also became apparent that hydrolysis of the final perfusates invariably gave a moderate but definite increase in the reducing substance. After deducting this amount of reducing substance recovered by hydrolysis, the amount of dextrose utilized by the heart in these experiments exceeded considerably that utilized by the heart alone. This is indicated in the tables and figures. In no instance did the control perfusion show any variation in reducing sugar beyond the limits of experimental error. From these experiments, then, it seemed that the pancreas not only enabled the heart in some direct way to utilize dextrose, but some alteration in the dextrose also occurred whereby it was changed in part at least to a non-reducing form which could be transformed back to dextrose again by hydrolysis.

WAS THIS UTILIZATION OF DEXTROSE A TISSUE EXTRACT PHENOMENON?

Was the disappearance of dextrose when the heart and pancreas were perfused together an effect similar to that obtained when muscle and pancreas extracts are allowed to act on dextrose? A number of heart-pancreas perfusions, which were considered as failures because the heart stopped beating soon after the perfusion was begun, showed practically no utilization of dextrose. The results of four such experiments are given in Table VII. In Experiment 36 the heart stopped beating almost immediately at the beginning of the perfusion. In Experiment 62 the heart and pancreas were frozen on removal from the body and then perfused. In Experiments 43 and 45 the pancreas was removed and ground, with all aseptic precautions, extracted with Locke's solution, and filtered. The hearts were then perfused with this extract. The hearts stopped beating almost instantly, and the perfusion pressures rose to over 250 mm. of mercury. The perfusions were continued above this pressure, however. In none of these four experiments was there any disappearance of dextrose over a four-hour period.

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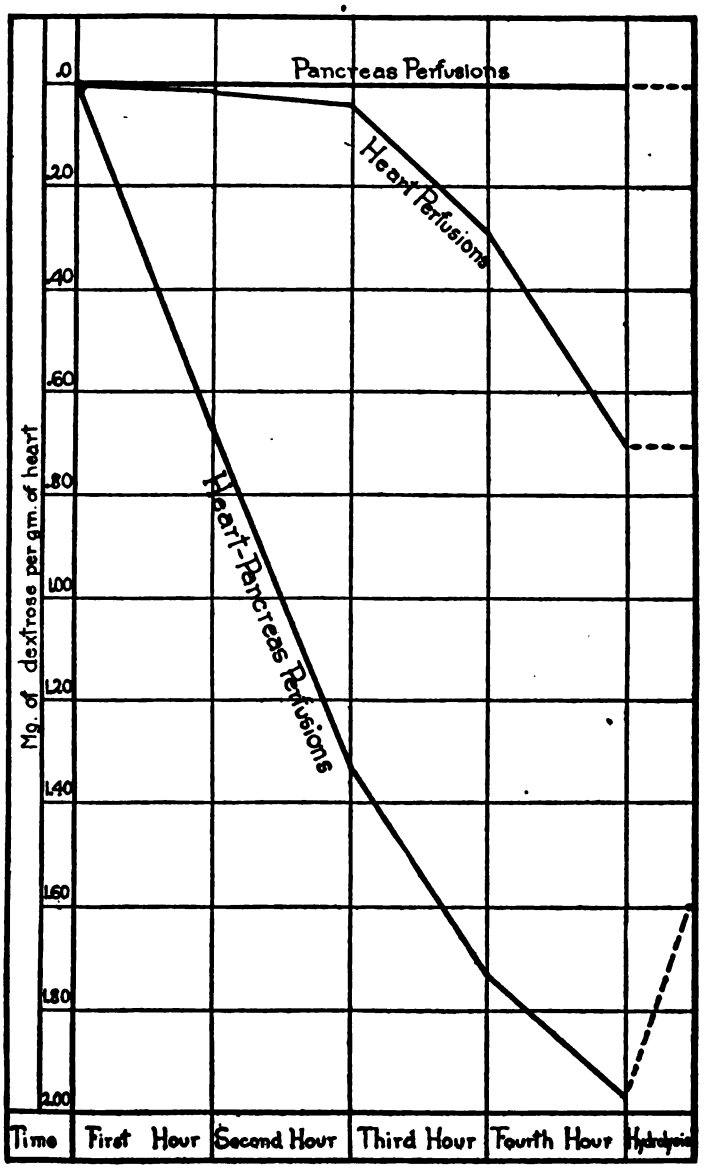

Fig. 2.—Curves showing the utilization of dextrose when the pancreas is perfused alone, when the heart is perfused alone, and when the two are perfused simultaneously. Note the increase in reducing substance in the heart-pancreas perfusions on hydrolysis.

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TABLE VII.

THE EFFECT OF PANCREATIC PERFUSATES AND PANCREATIC EXTRACTS ON NON-BEATING HEARTS.

Experiment No.	Procedure of experiment.	Weight of heart.	Dextrose after 10 min. perfusion.	1st hr.			2d hr.			3d hr.			4th hr.		
				Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.
		gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*	
36	Non-beating heart-pancreas perfusion.....	80	0.100	0.100	0	4	0.099	0	0	0.099	0	0	0.100	0	0
43	Non-beating heart perfused with pancreas extract	106	0.200										0.200	0	0
45	Non-beating heart perfused with pancreas extract	94	0.146										0.145	0.002 per hr.	1,260
62	Heart and pancreas frozen, then perfused.	165	0.199	0.200	0		0.200	0		0.200	0		0.200	0	

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Again, in all the heart-pancreas perfusions reported above, and others to be mentioned below, the final perfusates were placed in the thermostat with chloroform and toluene as preservatives. If the dextrose utilization had been due merely to the extracts of the heart and pancreas, the disappearance of dextrose ought to continue in the fluid after perfusion. It was invariably found, however, that not only was there no subsequent disappearance of dextrose in these perfusates, but that they generally showed an increase in the amount of reducing substance present. The immediate cessation of glycolytic action was probably not due to the preservatives used, for the experiments of most of the workers from Cohnheim to Levene and Meyer have been based on the effect of tissue extracts preserved with similar antiseptics. It is also to be emphasized that if the disappearance of dextrose was due to the tissue extracts, some change might be expected in the control perfusions which had passed for 10 minutes through the vessels of the two organs. The control perfusions, however, did not show any change, and this fact is discussed further below. Finally, in the experiments of Levene and Meyer[14] this phenomenon occurred only with strengths of dextrose greatly in excess of the physiological amounts used in these experiments, and on hydrolysis they were able to obtain practically all the original sugar. In my experiments only a small portion of the reducing substance could be recovered by hydrolysis. It is believed, therefore, that the results of these experiments indicate that the utilization of dextrose in the heart-pancreas perfusions in which the heart was actively beating was not a phenomenon similar to that obtained when muscle and pancreas extracts are allowed to act on more concentrated solutions of dextrose, but that in these experiments the utilization of dextrose was dependent on the activity of the living heart tissues.

THE PANCREAS FIRST PERFUSED AND SUBSEQUENTLY THE HEART PERFUSED WITH THE SAME SOLUTION.

The question next arose as to whether the pancreas supplied anything to the perfusing Locke's solution which could subsequently cause the utilization of dextrose by the heart. Six experiments were conducted to determine this point. The results are given in Table VIII, and charted in Fig. 3. In Experiments 40 and 42 the pancreas was first perfused for one hour with Locke's solution containing dextrose. The dog was meanwhile kept alive under light ether anesthesia. The

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TABLE VIII.

EXPERIMENTS IN WHICH THE HEART WAS PERFUSED WITH A SOLUTION WHICH HAD PREVIOUSLY BEEN PERFUSED THROUGH THE PANCREAS. IN THE LAST FOUR EXPERIMENTS THE PANCREAS WAS PERFUSED WITH LOCKE'S SOLUTION CONTAINING NO DEXTROSE. AFTER REMOVAL OF THE PANCREAS SUFFICIENT DEXTROSE WAS ADDED TO THE PERFUSATE TO GIVE THE DESIRED PER CENT.

Experiment No.	Length of time pancreas perfused.	Dextrose utilized by pancreas.	Weight of heart.	Dextrose after 10 min. heart perfusion.	1st hr.			2d hr.			3d hr.			4th hr.			Dextrose per gm. of heart recovered by hydrolysis.
					Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	
			gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*
40....	1 hr.	0	82	0.100	0.091	0.277	12	0.077	0.41	220	0.064	0.38	164	0.048	0.600	64	0.422
42....	1 "	0	81	0.199	0.167	0.99	5	0.153	0.442	36	0.153	0	121	0.123	0.87	3	0.5
44....	40 min.	0	119	0.297	0.160	2.76	0	0.133	0.555	0	0.109	0.40	1	0.092	0.28	5	0.43
46....	15 "	0	91	0.246	0.176	2.1	0	0.170	0.158	0	0.121	1.22	0	0.109	0.28	0	0.94
47....	40 "	0	105	0.096	0.072	0.63	0	0.059	0.386	0	0.051	0.17	0	0.051	0	0	0.465
48....	40 "	0	105	0.30	0.272	0.761	0	0.24	0.605	0	0.217	0.422	0	0.171	0.86	0	0.55

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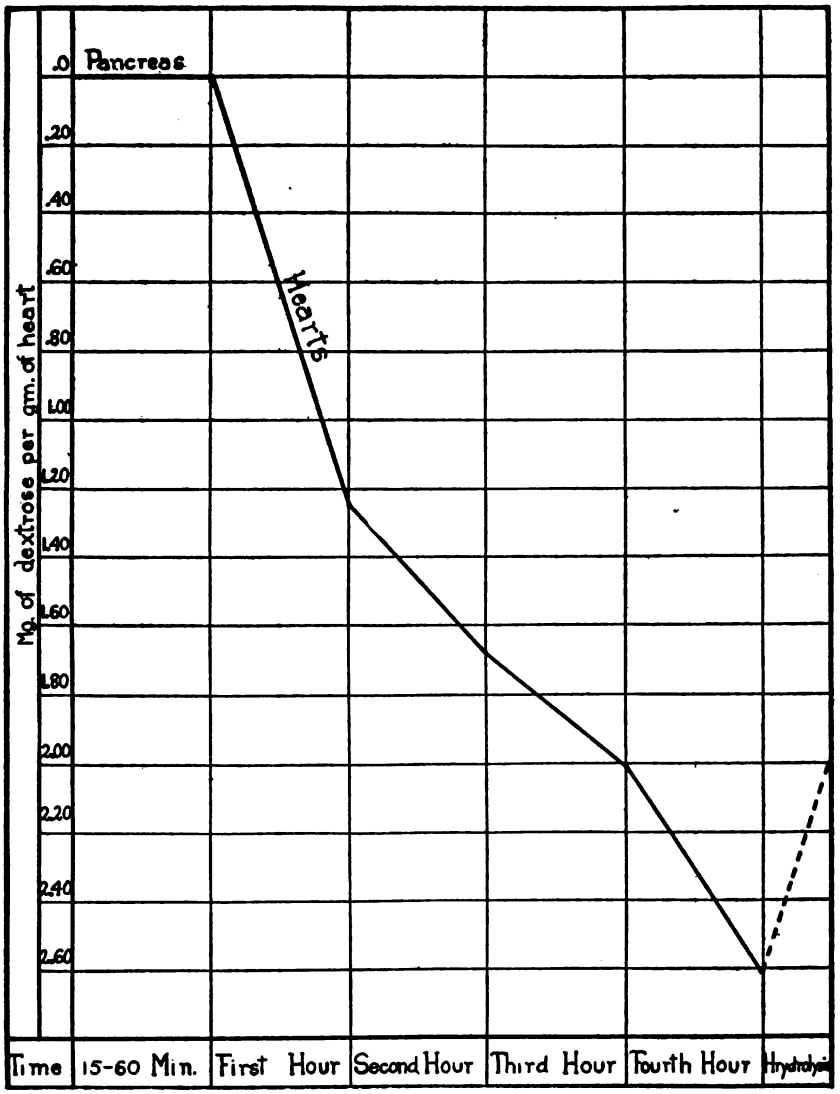

FIG. 3.—The average curve of the six experiments in Table VIII. The pancreas was first perfused for periods varying from 15 to 60 minutes; it was then removed from the apparatus and the heart of the same dog substituted. There was no dextrose utilization by the pancreas, but when the heart was subsequently perfused with the fluid which had been perfused through the pancreas, the heart-pancreas type of dextrose utilization occurred.

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pancreas was then removed from the apparatus, and the heart substituted and perfused with the same solution that had been perfusing through the pancreas. The utilization of dextrose by the heart proceeded exactly as if the pancreas were in circuit, and hydrolysis of the final prefusate gave an increase in the reducing substance. Four experiments were then carried out in which the pancreas was first perfused for a period of 15 to 40 minutes with a Locke's solution containing no dextrose. The pancreas was then removed from the apparatus and sufficient dextrose added to the perfusing solution to give approximately the desired percentage. After allowing it to mix thoroughly in the apparatus, perfusion of the heart was begun. Again all the experiments showed rapid dextrose utilization and, as in the heart-pancreas perfusions, hydrolysis of the final perfusates increased their reducing properties. Two facts thus seemed evident. First, the pancreas did not alter the reducing properties of the dextrose passing through its vessels. Second, the pancreatic factor causing the rapid disappearance of sugar was contained in the perfusate and continued to act after removal of the pancreas. The pancreas, therefore, had furnished some constituent to the perfusing liquid which greatly accelerated the utilization of sugar by the heart muscle.

EFFECT OF HEAT ON PANCREATIC PERFUSATES.

If this pancreatic factor accelerating dextrose utilization by the heart is an enzyme, it should be affected by heat; while if it has a more stable character, like adrenalin, it should not be affected by heat to any extent. The five experiments on this point are tabulated in Table IX and shown in Fig. 4. In all the experiments the pancreas was perfused for 30 minutes and the perfusate was then removed from the apparatus. After completion of the pancreas perfusion the apparatus was carefully washed and sterilized in the steam sterilizer for 30 minutes. The heart was then perfused with the pancreatic perfusate which meanwhile had been subjected to various degrees of heating. In Experiments 51 and 52, the pancreatic perfusate was just brought to the boiling point and cooled; in Experiment 55 the perfusate was boiled for 10 minutes. In Experiments 53 and 54 the pancreatic perfusates were heated to 56° C. for 30 minutes on a water bath, then cooled and perfused through the heart. In all these experiments the heart continued to beat during the four-hour period. The results were definite, as shown in Fig. 4. When the pancreatic

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TABLE IX.

CONDENSED TABLE OF EXPERIMENTS SHOWING THE EFFECT OF HEAT ON THE PANCREATIC PERFUSATE.

Experiment No.	Pancreas perfused 30 min. Perfusate removed and apparatus sterilized. Heart then perfused with pancreatic perfusate treated as follows:	Dextrose utilized by pancreas.	Weight of heart.	Dextrose after 10 min. heart perfusion.	1st hour.			2d hour.			3d hour.			4th hour.			Dextrose per gm. of heart recovered by hydrolysis.
					Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	
			gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*
51	Pancreas perfusate brought to boiling temperature.	0	50	0.119	0.119	0	0	0.108	0.523	0	0.093	0.139	9	0.085	0.204	4	0.03
52	Pancreas perfusate brought to boiling temperature.	0	63	0.120	0.120	0	0	0.120	0	0	0.120	0	0	0.099	0.711	9	0
55	Pancreas perfusate boiled for 10 min.	0	62	0.200	0.199	0	5	0.200	0	6	0.196	0.14	..	0.188	0.254	34	0
53	Pancreas perfusate heated to 56° C. for 30 min.	0	72	0.200	0.154	1.55	1	0.137	0.563	0	0.126	0.337	4	0.113	0.496	17	0.71
54	Pancreas perfusate heated to 56° C. for 30 min.	0	60	0.200	0.166	1.35	1	0.153	0.496	2	0.133	0.733	5	0.125	0.286	3	0.86

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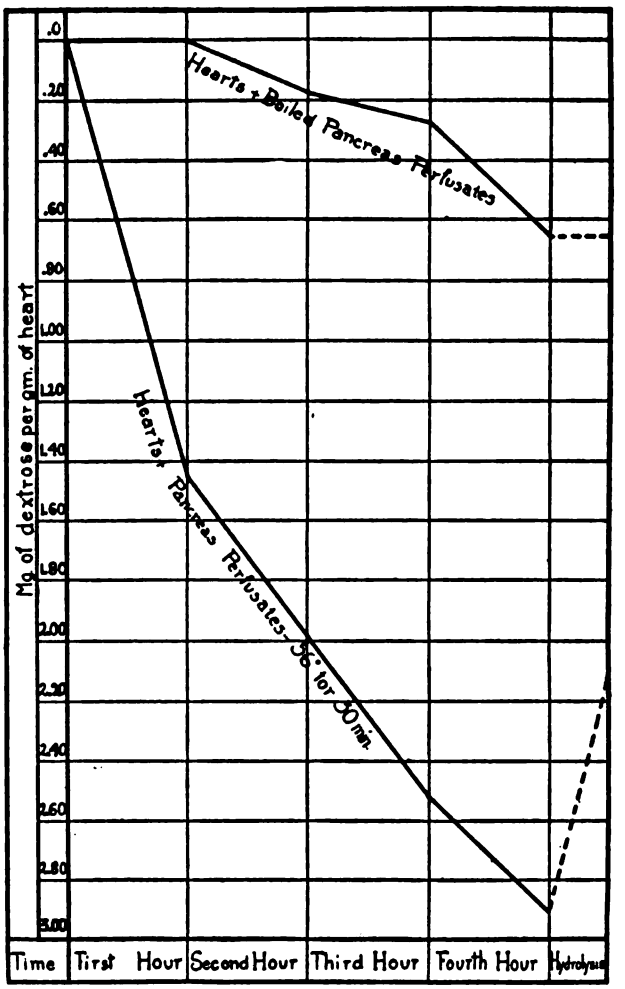

FIG. 4.—Chart of Table IX showing the effect of heat on the pancreatic perfusates. The upper curve shows the utilization of dextrose in the experiments in which the pancreatic perfusate was heated to boiling and cooled before perfusion through the heart. The lower curve shows what occurred when the pancreatic perfusate was only heated to 56° C. for 30 minutes.

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perfusate was heated to boiling it lost its power of enabling the heart to utilize dextrose. The utilization of dextrose proceeded practically as if the heart were being perfused alone. Heating the pancreatic perfusate to 56° C. for 30 minutes, however, did not cause any inactivation. Subsequent perfusion through the heart gave the typical heart-pancreas type of dextrose utilization. These experiments, therefore, indicated that the pancreatic factor has the characteristic of an enzyme in being inactivated by boiling temperature.

AMOUNT OF PANCREATIC PERFUSATE NECESSARY TO ENABLE THE HEART TO UTILIZE DEXTROSE.

In the experiments shown in Table VIII in which the pancreas was first perfused and the same solution was subsequently perfused through the heart, the entire pancreatic perfusate of 250 c. c. was used. The question arose as to the minimum amount of pancreatic perfusate necessary to enable the heart to utilize dextrose immediately. Four experiments were carried out, as shown in Table X, and Fig. 5. The pancreas was first perfused with 250 c. c. of Locke's solution containing 0.2 per cent of dextrose. This perfusate was then removed and the apparatus was washed and sterilized for 30 minutes to inactivate any adherent pancreatic substance. The heart of the same animal was then perfused with a fresh solution to which varying amounts of the pancreatic perfusate had been added, the total volume of the perfusate being made up to 250 c. c. As seen in the curves of Fig. 5, when 10 c. c. of the pancreatic perfusate were added, the curve of dextrose utilization by the heart is practically the same as if the entire 250 c. c. had been used. Hydrolysis of the final perfusates, however, did not give as definite an increase in reducing substance as in the typical heart-pancreas perfusions. When 5 c. c. and 1 c. c. were used, though the utilization of dextrose began within the first hour, it did not proceed as rapidly as when the larger amounts were used. These experiments indicate that even 1 c. c. of a 250 c. c. pancreatic perfusate added to 249 c. c. of Locke's solution has a distinct effect in enabling the heart to utilize dextrose immediately.

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TABLE X.

RESULTS OF EXPERIMENTS TO DETERMINE THE AMOUNT OF PANCREATIC PERFUSATE NECESSARY TO ENABLE THE HEART TO UTILIZE DEXTROSE IMMEDIATELY.

Experiment No.	Pancreas perfused 30 min. Perfusate removed and apparatus sterilized. Heart then perfused with the following mixtures.	Dextrose utilized by pancreas.	Weight of heart.	Dextrose after 10 min. heart perfusion.	1st hour.			2d hour.			3d hour.			4th hour.			Dextrose per gm. of heart recovered by hydrolysis.
					Dextrose	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per gm. of heart.	Bacteria per c. c.	
			gm.	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*
49	Pancreatic perfusate 10 c. c. Locke's solution 240 "	0	70	0.265	0.176	3.07	0	0.173	0.122	0	0.165	0.244	0	0.149	0.49	0	0
50	Pancreatic perfusate 10 " Locke's solution 240 "	0	119	0.284	0.175	1.76	0	0.157	0.27	0	0.158	0	0	0.158	0	0	0.248
57	Pancreatic perfusate 5 " Locke's solution 245 "	0	83	0.200	0.153	1.41	27	0.143	0.316	5	0.142	0.011	25	0.141	0.032	128	0.083
59	Pancreatic perfusate 1 " Locke's solution "	0	75	0.200	0.182	0.564	0	0.183	0	0	0.166	0.50		0.154	0.37	89	0

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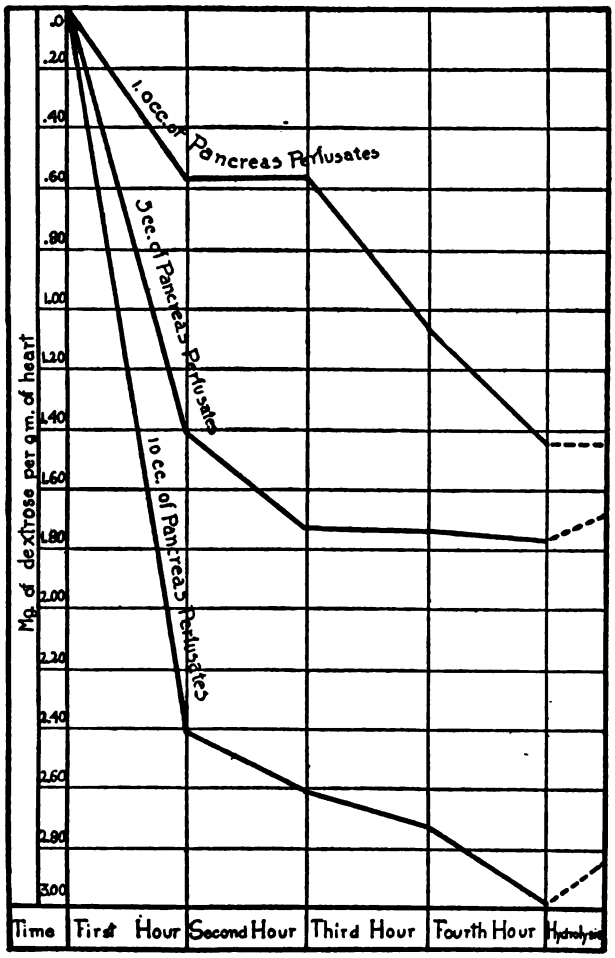

Fig. 5.—Chart of Table X showing the result of adding different amounts of the pancreatic perfusate to a perfusion of the heart from the same dog.

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INSTABILITY OF THE PANCREATIC PERFUSATE AFTER PERFUSION.

It was hoped to carry out a number of other experiments which would depend on the ability of the pancreatic perfusate to maintain its activity when kept for 24 hours or more without a preservative. To test this, three experiments were carried out. The figures are shown in Table XI. A pancreas was perfused with 250 c. c. of Locke's solution for 30 minutes and the perfusate was placed on ice for 48 hours in one experiment and 24 hours in two experiments. At the end of that time the heart of another dog was perfused with the entire pancreatic perfusate, but with the result that only the heart type of dextrose utilization occurred. It hardly seemed probable that this could be due to the fact that different dogs were used, but rather that the enzyme-like substance had lost its activity during these short periods of time. That the perfusates used were originally fully active was demonstrated by the fact that they were the perfusates which had previously been shown to be highly active.

THE LATENCY OF SUGAR UTILIZATION.

An interesting finding which should be mentioned is the fact that in the heart-pancreas perfusions no dextrose utilization ever seemed to have occurred in the first 10 minutes of perfusion, the period which was allowed to elapse before filling the control apparatus. If the dextrose had been used by the heart in this time at the same rate that it was used in the following hour, the utilization should at least have been evident. Even in the experiments where the pancreas was first perfused and the heart subsequently perfused with the same fluid, there was no evident utilization of sugar during the first 10 minutes. In such experiments the hearts must have been supplied immediately with an abundance of the pancreatic enzyme. From my experiments it cannot be stated how much more than 10 minutes elapsed before utilization of dextrose began, for an hour was allowed to pass before making another reading. It would seem, therefore, that there is a certain latent period before the heart begins to use dextrose, even though the dextrose is accompanied by an abundance of the pancreatic enzyme.

SUMMARY.

The experiments indicate that the pancreas, when perfused aseptically with Locke's solution containing physiological concentrations of dextrose, does not alter the reducing properties of the perfused

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TABLE XI.

EXPERIMENTS TO DETERMINE WHETHER THE PANCREATIC PERFUSATE WHEN ALLOWED TO STAND IN THE ICE BOX LOSES ITS POWER TO ENABLE THE HEART TO UTILIZE DEXTROSE IMMEDIATELY.

Experiment No.	Heart perfused with pancreatic perfusate from experiment No.	Pancreatic perfusate in ice box.	Weight of heart.	Dextrose after 10 min. heart perfusion.	1st hour.			2d hour.			3d hour.			4th hour.			Dextrose per Gm. of heart recovered by hydrolysis.
					Dextrose.	Dextrose disappeared per Gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per Gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per Gm. of heart.	Bacteria per c. c.	Dextrose.	Dextrose disappeared per Gm. of heart.	Bacteria per c. c.	
		hrs.	*gm.*	*per cent*	*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*per cent*	*mg.*		*mg.*
56	54	48	59	0.200	0.200	0	4	0.184	0.27	28	0.166	0.20	344	0.151	0.18	824	0
58	57	24	56	0.200	0.200	0	980	0.200	0	220	0.167	1.33	312	0.148	0.777	920	0
60	59	24	54	0.195	0.191	0.18	54	0.183	0.32	12	0.154	1.22	9	0.138	0.69	44	0

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solution. The pancreas, however, seems to supply something to the Locke's solution circulating through its arteries, which in some way brings about a utilization of sugar by the living heart to an extent that does not occur with the heart alone. This pancreatic substance possesses some of the characteristics of an enzyme. It is inactivated by boiling; it is unstable, rapidly becoming inactive on standing; it acts in small amounts; it causes a great acceleration in the rate of a reaction which otherwise proceeds slowly, and the rate of reaction diminishes as the reaction proceeds. Thus this substance has more of the characteristics of an enzyme than of a stable internal secretion like that of the adrenal glands. The disappearance of sugar was dependent upon the presence of living heart tissue, and it ceased as soon as the perfusate was removed from the heart-pancreas circulation, and did not occur at all when a pancreatic perfusate was passed through a non-beating heart. This result indicates that the reaction is not similar to that obtained when muscle and pancreas extracts act on more concentrated solutions of dextrose.

The living heart, in the presence of the pancreatic factor and dextrose, is responsible for two effects. First, a condensation of the sugar to a non-reducing form that yields again a simple sugar on hydrolysis, or by simply standing, with a preservative, at 37° C. for 24 hours. Second, a disappearance of sugar which is probably due to its destruction by hydrolysis or oxidation. After deducting the reducing sugar in the heart-pancreas perfusions which could be recovered by hydrolysis, the amount of sugar which had actually disappeared exceeded that which was used by the heart when perfused with dextrose alone. As to the fate of this portion of the sugar, no definite evidence was obtained.

The question arises as to whether this substance obtained from the perfused pancreas is identical with the hypothetical internal secretion of the pancreas so essential in sugar metabolism. That there is an internal secretion of the panceras which can be obtained by this method, and that in some way it accelerates the utilization of sugar by the living heart, seems evident. Though the conclusions are based on the heart and pancreas isolated from the numerous interrelating factors occurring in the body, the evidence suggests at least that the substance or substances obtained by perfusing the pancreas may be concerned in the normal activity of the pancreas upon sugar metabolism.

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CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA: ASSOCIATED WITH FUSED KIDNEY.

A CASE REPORT AND A SURVEY OF THE LITERATURE ON CONGENITAL ANOMALIES OF THE ESOPHAGUS.

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INTRODUCTION.

Congenital anomalies of the esophagus that result in death shortly after birth are relatively rare, and are of considerable interest both clinically and pathologically. Associated anomalies in other organs are frequent. The following case was observed within the past year, and furnished the basis for a study of esophageal malformations based upon a thorough search of the literature. It represents the most common form of malformation of the esophagus, and the history and findings are quite typical of the group.

CASE REPORT.—Baby L. (Gen. No. 106,455, Obst. No. 7571) was born at 10.30 a. m., Dec. 2, 1915. The presentation was R. M. A., but the child was born spontaneously after a left-sided episiotomy. The mother was a 34-year-old primipara who had last menstruated on Feb. 22, 1915. She had suffered from a mild toxemia (pre-eclamptic) during the last week of her pregnancy, which had been otherwise uneventful. Both the mother and the father presented negative Wassermann tests. The pelvis was normal and the labor lasted eight and one-half hours. There was a post-partum hemorrhage of 900 c. c.

The child was a female, 48.5 cm. long and weighed 2650 gm. It was slightly asphyxiated at birth but was resuscitated without difficulty. The face was markedly swollen and discolored and considerably bruised with an abrasion of the skin radiating from the left corner of the mouth. No external abnormalities were noted. The child was rather small but seemed vigorous and healthy.

Because of the edema and bruising of the face, the child was not put to the breast until 24 hours after birth. During the interval it was noted that there was an excess of mucus in the throat which periodically impeded respiration and produced alarming cyanosis. At the first nursing the child took the breast well but immediately regurgitated everything swallowed. It was still thought that this might be due to edema of the deeper

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structures. In order to ascertain whether any milk was being retained, the child was weighed before and after nursings and no increase in weight was noted. On Dec. 5 an attempt was made to feed by gavage; but the tube was arrested 12.0 cm. from the gums. A soft rubber 3 mm. and a stiff silk catheter were tried with like results. The child could swallow 4.0 or 5.0 c. c. (three medicine-dropperfuls) of milk and would then regurgitate it all. The regurgitation was frequently associated with a good deal of coughing.

Examination of the chest at this time showed the percussion note dulled, more on the right side. There were coarse loud râles and groans over both fronts and backs. It was noted that the breath sounds could be heard unusually plainly over the abdomen. With a small bronchoscope the esophagus was examined but no opening below could be found; the trachea could not be inspected because of the profuse secretion of mucus. Meconium was passed quite regularly and urine was voided normally in small amounts. The temperature became elevated 48 hours after birth and continued above normal until the time of death. At 11.00 p. m., Dec. 5, a gastrostomy was performed without anesthesia. An ounce of milk placed in the stomach immediately afterward was retained. The following morning, when the stomach was washed out through the tube preparatory to feeding, the fluid introduced ran out of the mouth and nose. This was accompanied by a violent coughing spell and marked cyanosis. The respirations became very shallow and rapid and the weakened child died at 11.45 a. m., four days after birth.

The autopsy was performed at 1.30 p. m. the same day.

Autopsy No. 4527.—The body is that of a four-day-old female child. In the upper abdomen slightly to the left of the median line there is a fresh operative wound, 3.0 cm. long, through which passes a small rubber tube. There are many fairly firm, new adhesions between the stomach and the anterior abdominal wall in the region of the incision. The organs are normally disposed. The liver extends 4.0 cm. below the costal margin. The pleural cavities are free. The thymus is small and appears normal. The thoracic and abdominal organs were removed *en masse*. The bronchi were tied off near the lungs, the operation wound in the stomach was closed, the duodenum was severed and 15 per cent gelatin with Berlin blue was injected through the pylorus and through the upper end of the esophagus. The specimen was cooled, hardened in No. 1 Kaiserling solution and after two days was dissected.

Heart and great vessels, normal.

Lungs, normal in size, shape and position, with the usual division into lobes. Well distended with air. The surface has a deep reddish-purple color mottled with light grayish-pink areas which are more numerous near the free edges. On cut section the same appearances are noted.

Kidneys.—The two kidneys are fused along their entire median border and lie approximately in the mid-line with the great vessels passing through a depression on the posterior surface. The right kidney measures 4.8 x 2.8 x 1.0 cm.; the left 2.6 x 2.0 x .75 cm. The communicating portion

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is 2.5 cm. long and only a few millimeters in thickness. There are two ureters emerging from the anterior surfaces of the respective portions of the kidney. The left ureter passes outward toward the right side crossing the median line and then, just below the lower pole, swings back to its usual position. The blood supply is derived from two arteries which enter near the upper pole and from one artery which enters the lower pole in the median connecting portion.

Liver, pancreas, spleen, adrenals, intestines and genitalia, normal.

Head—brain removed. Sutures very tight, fontanelles small. No hemorrhages present.

Microscopic examination: Lungs.—The alveoli are generally well expanded and many of them contain a homogeneous-appearing, foreign material which stains with hematoxylin. There is no inflammatory reaction and no evidence of bronchopneumonia except a marked congestion of the smaller vessels.

The other organs are normal.

Esophagus and trachea.—The upper portion of the esophagus ends blindly 4.0 cm. below the larynx and 1.7 cm. above the bifurcation of the trachea. It is considerably dilated and has a diameter of 1.75 cm. Its walls are somewhat hypertrophied. The lower portion leaves the stomach and goes through the diaphragm normally. It passes up slightly to the left but gradually approaches the mid-line and enters the trachea 5.0 mm. above the bifurcation. Its diameter is 9.0 mm. at its lower end and 4.0 mm. at the tracheal end; the greatest diameter being 13.0 mm. a little above the diaphragm. The opening in the trachea is 11.0 x 4.5 mm. in size. There is no dilatation and no hypertrophy of the walls. Careful dissection failed to reveal any connection between the two segments.

Diagnosis.—Congenital atresia of the esophagus with communication between the esophagus and the trachea.

Fused kidney (*Ren informis*).

The case cited above led to a survey of the literature on the subject of congenital anomalies of the esophagus, and it was soon found that, while there were many reports of cases and incomplete bibliographies, a considerable confusion existed and made the search rather difficult. Moreover, there was nowhere a comprehensive bibliography in English, although Griffith and Lavenson gave a fairly inclusive list in 1909. The discovery of many errors in the various lists made it advisable to prolong the search in an effort to consult the original article in each case. It is not expected that all the reports have been found, but certainly very few have been missed and many errors have been eliminated. During the search many reports of other early-fatal anomalies in the development of the esophagus were discovered and are placed in supplementary lists, according to the conditions present.

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Survey of the Literature.

History.—It is usually stated that the first published case of this anomaly is that recorded by Martin in 1821, but W. Thomas cites a case which was observed in 1696 by Thomas Gibson. I have been able to verify this reference, and the account is so quaint and so typical that I quote it verbatim.

About November, 1696, I was sent for to an infant that could not swallow. The child seemed very desirous of food and took what was offered it in a spoon with greediness, but when it went to swallow it, it was like to be choaked; and what should have gone down, returned by the mouth and nose, and it fell into a struggling convulsive sort of a fit upon it. It was very fleshy and large and was two days old when I was called to it but the next day died.

The parents being willing to have it opened, I took two physicians and a surgeon with me. On opening the abdomen first, the guts had some of the meconium remaining still in them, though the child had gone two or three times to stool. The stomach had in it a pretty deal of a slimy sort of liquid (or gelly rather), somewhat like thick (strained) water-gruel. I shall not mention any observation upon other parts of the abdomen, as being not to our present purpose.

Then we cut open the thorax and taking out the gullet (with the wind-pipe, lungs, etc.) continued to the stomach. Then we made a slit in the stomach and put a pipe in its upper orifice, and blowing, we found the wind had a vent, but not by the top of the gullet. Then we carefully slit up the back side of the gullet from the stomach upwards, and when we had gone a little above half way toward the pharynx we found it hollow no further. Then we began to slit it open from the pharynx downwards, and it was hollow till within an inch of the other slit, and in the imperforate part it was narrower than in the hollowed. This isthmus (as it were) did not seem ever to have been hollow, for in the bottom of the upper and the top of the lower cavity there was not the least print of any such thing, but the parts were here as smooth as the bottom of an acorn cup.

Then searching which way the wind had passed when we blew from the stomach upwards, we found an oval hole (half an inch long) on the fore side of the gullet opening into the aspera arteria, a little above its first division, just below the lower part of the isthmus above mentioned.

Now, I say, this is a plain confirmation of the fœtus's being nourished by the mouth; for the gula being impervious, Nature had formed this hole in the wind-pipe and gullet for the liquor contained in the amnios to pass into the stomach, which it might do without prejudice, or any fear of choaking in the womb, while the child breathed not; but when it was born and came to breathe, there could be no longer any passage this way, and so the infant was necessarily famished.

In 1861 Hirschsprung reported four cases of his own and collected 10 other cases from the literature.

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Mackenzie, in 1880, was able to find reports of 42 cases in which the upper portion of the esophagus had ended blindly and the lower portion had entered the trachea (39 cases) or a bronchus (three cases). He stated that every reference had been verified personally, but evidently failed to take into account the fact that several cases had been reported by two different observers, and in reality he offers only 37 distinct cases and four of these are rather doubtful museum specimens.

Legrand found 46 cases in 1897; in 1905 Kreuter collected 65 and Happich 57 cases. Four years later, Griffith and Lavenson were able to add 14 cases to Happich's list, making 71 in all.

Results of the Present Compilation.—By taking advantage of all the published bibliographies, I have been able to collect more than double the number of cases referred to by Griffith and Lavenson. In 136 cases I have actually consulted and verified the reference to the original article, and in addition have found 13 cases referred to by various authors, which could not be verified because of inaccurate references or the inaccessibility of the original article. In six cases the clinical findings made the diagnosis practically certain, but no autopsy was performed or at least no report of the post-mortem findings was presented. In several reports the authors mention other similar cases seen by them but not recorded.

The following paragraphs are based upon the evidence offered by the case reports which have been actually consulted. The unverified cases have not been employed in compiling the statistics, but in the bibliography they will be noted under suitable headings. Museum specimens are usually under suspicion because so many of them have been described elsewhere than in the museum catalogue. The few museum specimens which have been included in the verified list are those that almost certainly have not been recorded elsewhere.

Pathological Anatomy.—The cases vary in the minor details relating to the anomaly, but in general the picture is quite uniform. The upper portion of the esophagus ends in a cul-de-sac at varying distances below the larynx and above the tracheal bifurcation. In 72 cases the length of the upper cul-de-sac below the larynx is noted as follows:

Cul-de-sac 1.0 to 1.9 cm. long	5
Cul-de-sac 2.0 to 2.9 cm. long	14
Cul-de-sac 3.0 to 3.9 cm. long	24
Cul-de-sac 4.0 to 4.9 cm. long	20
Cul-de-sac 5.0 cm. and over	9
	72

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The pouch is usually but not always dilated, so that its circumference is somewhat greater than that of the normal esophagus and its walls are usually hypertrophied. This dilatation and hypertrophy are evidently the result of the ineffectual attempts of the fetus to swallow the amniotic fluid. Occasionally, as in the cases of Rasmussen and von der Water, there is a fistulous communication between this upper portion and the trachea.

The lower portion leaves the cardia and ascends in its usual position until it enters the trachea at or somewhat above the bifurcation, or, more rarely, one or the other bronchus. In 96 cases where the point of entrance into the respiratory tract is noted we find the following:

Opening into a bronchus	2
Opening into trachea at the bifurcation	33
Opening into trachea between bifurcation and point 0.5 cm. above.	33
Opening into trachea from 0.6 to 1.0 cm. above bifurcation	12
Opening into trachea from 1.1 to 2.0 cm. above bifurcation	18

At its cardial end the esophagus is usually of normal size, but frequently diminishes in caliber as it ascends and enters the trachea by a minute opening.

The two portions may or may not be connected by a thin strand of tissue. Thus, in the list of 136 cases, such a communication was noted in 51, while in 41 it was said to have been absent, and in the remaining 44 there was no note concerning its presence. In 26 of the 51 cases it consisted of muscle fibers; in 13 it was fibrous; in three connective tissue, and in the remaining nine it was merely called a "strand of tissue." It would seem that some connection should always exist, but in many cases, as in the one herewith reported, no such band could be demonstrated.

The tracheal opening varies in size with the diameter of the upper portion of the lower segment. The edges of the openings are always smooth, and the mucous membrane of the two tubes is uninterrupted. The muscular walls of the two passages frequently blend without any line of demarcation. Occasionally rudimentary tracheal cartilages have been found in the tracheal portion of the esophagus.

Other anomalies of development are frequently present. In this series their presence or absence was noted in 94 cases, and in 59 of these they were present (patent foramen ovale and ductus arteriosus are not classed as anomalies). By far the most frequent associated abnormity is atresia ani; it was noted in 24 cases.

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The presence of an increased amount of amniotic fluid (hydramnios) was noted in only nine cases, and this condition seems to be a mere coincidence rather than a result of the inability of the fetus to swallow the fluid and eliminate it by the blood stream. On the other hand, the dilatation and hypertrophy of the upper cul-de-sac are evidences of an attempt to swallow. The logical deduction from these two observations is that normally the quantity of fluid is regulated by absorption through the gastro-intestinal tract, but that, when this fails, absorption takes place through some other channel, or the formation of fluid is checked. Gibson's theory that the child swallows the fluid by way of the trachea seems hardly tenable, in view of the fact that lanugo hairs are usually absent from the meconium and that hydramnios is no more common in the cases of atresia without an associated tracheo-esophageal fistula.

Etiology.—It is now generally conceded that the anomaly is due to a developmental error rather than to an intra-uterine inflammatory process, as was at one time argued. It must arise at a very early stage in the development of the fetus, because in 4.0 mm. long embryos the trachea is quite separate from the esophagus. In the Harvard Embryological Collection there is an embryo only 18.1 mm. long which shows the abnormity. Keibel and Mall say: "To produce the common form of the anomaly, the lower portion of the tracheo-esophageal septum must fail to develop, thus leaving the esophagus in communication with the lower part of the trachea." Zeit says: "Arrested development of the lateral ridges which unite incompletely in the mid-line, as the lateral tracheal and dorsal esophageal tubes are forming, would explain the fistula but not the atresia. In order that both atresia and fistula be caused by one factor, a faulty 'Anlage' with resultant malformation must have existed." Shattock's widely quoted explanation is as follows: "At the time when the pouch from which the lower air passages develop is formed from the anterior wall of the stomadeum, the posterior wall occasionally participates in the process sufficiently to be drawn forward, thus narrowing the lumen. When, subsequently, the lateral pouching for the formation of the larynx develops from the stomadeum just above this region, so much of the already narrowed lumen is consumed that the connection between the upper and lower portions is left communicating with the air passages." Keith and Spicer lay stress upon the presence of an anomaly of the great vessels in the thorax whereby there is present a right aortic arch and the left subclavian

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artery arises last from the arch of the aorta and passes behind the trachea just below the cul-de-sac of the esophagus thus reaching the left arm. This has been noted so rarely that it seems more probable that it is a concomitant anomaly rather than a causative factor.

No predisposing factors have been advanced and no two definite cases have been reported in the same family, although in a few instances it is stated that previous children had had some congenital abnormality. The father of the child reported by Morell Mackenzie stated that a former wife had given birth to a child which died after 19 days with exactly the same symptoms. In view of the long duration of life and the absence of other evidence, it seems probable that the condition was not the same.

In 37 cases the sex of the child is stated, and they are practically evenly divided—18 males and 19 females.

The abnormality apparently has little effect upon the duration of the pregnancy, for in 72 cases the child was said to be at term, in 22 premature, and in the remaining 42 there was no statement.

Symptoms.—The usual signs and symptoms are: (1) Asphyxiation at birth, due to mucus in the nose and throat; (2) choking attacks due to an accumulation of frothy, mucous saliva which cannot be swallowed; (3) regurgitation of all liquids after a small quantity has been swallowed; (4) inability to pass even the finest catheter (the height of the obstruction varies somewhat, but the catheter is usually arrested at a point 9.0 to 11.0 cm. from the alveolar margin); (5) the stomach is seen to inflate with each inspiration; (6) meconium is passed but there is no change in the evacuations even though the child lives for several days; examination of the meconium reveals the absence of lanugo hairs; (7) the breath sounds are more audible than normal over the abdomen; (8) rattling, whistling or noisy respirations frequently occur; (9) cyanosis, which recurs periodically, is quite a constant feature; (10) urine is voided as usual, but after a few days becomes minimal in amount.

Course of Events.—There is a progressive loss of weight, more marked during the first few days, and frequently accompanied by an elevation of temperature (inanition fever). If no complications arise, the child may live as long as 14 days, but in no case on record has life been prolonged for a greater period. There is great danger of bronchopneumonia developing as a result of the aspiration of infected material from the mouth, and many deaths are directly attributable to this dis-

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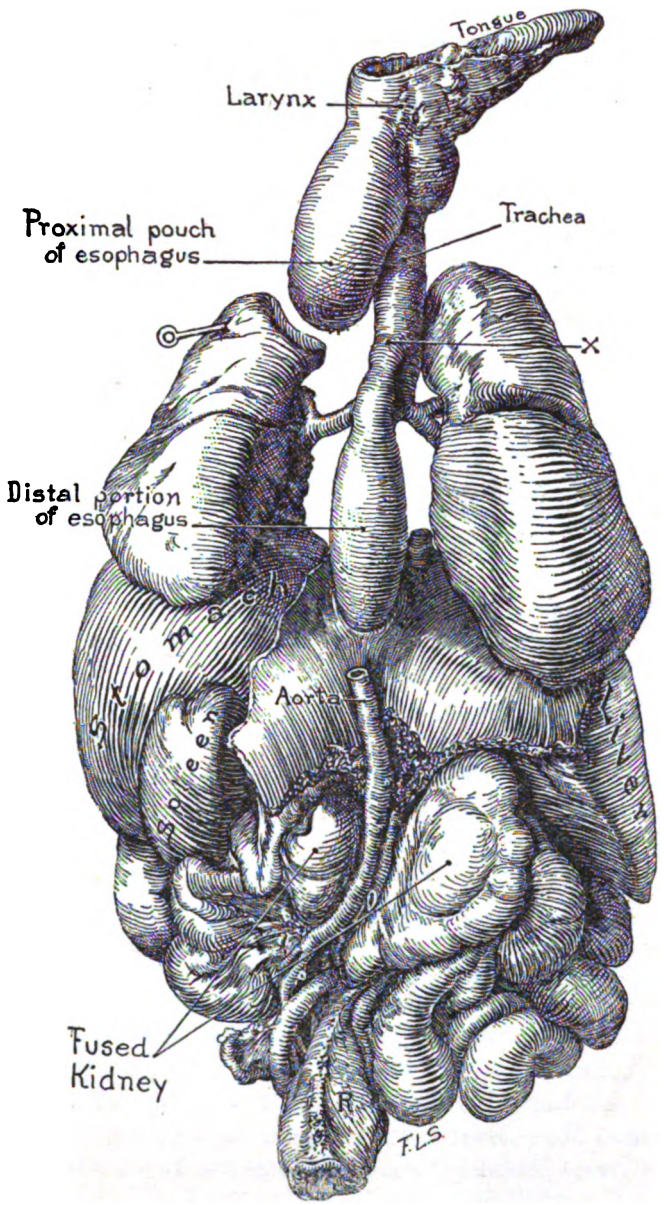

Viscera of the Present Case. (Posterior View.)

×=the point of entrance of esophagus into trachea. The stomach, trachea and esophagus have been injected.

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ease. It is evidenced by the usual signs and symptoms, which may be masked behind the respiratory symptoms due to the anomaly. In the weakened condition of the patient, this complication invariably hastens the fatal outcome. The day of death as given in the 136 cases considered is as follows:

Still-born 5	Sixth day 16	Eleventh day..... 4
First day..... 15	Seventh day..... 7	Twelfth day..... 1
Second day..... 18	Eighth day..... 6	Thirteenth day..... 1
Third day..... 13	Ninth day..... 4	Fourteenth day..... 1
Fourth day..... 14	Tenth day..... 3	Day not given..... 16
Fifth day..... 12		

Treatment.—No treatment has yet been devised that is of any permanent value. The only hope of rational therapy lies in advances of surgery within the thorax. The medical expedient of rectal feedings may prolong life for a few hours or days, but its possibilities are limited. Gastrostomy is absolutely futile as is attested by the 16 cases in which it has been tried without any success. Fundamentally, jejunostomy is a better procedure, because it obviates the back flow through the esophagus into the trachea which has been noted in the majority of the cases where feeding has been attempted through a gastrostomy wound. I can find only one case on record where a jejunostomy was performed and it was not a success. At best these procedures have little to recommend them, and until some method of attacking the lack of continuity of the esophagus has been devised, it seems better to allow the little patients to die as quietly as possible.

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ERRORS DISCOVERED IN PREVIOUS BIBLIOGRAPHIES.

In several instances the same case seems to have been reported independently by two or more observers, while in other instances typographical and other errors have been carried along from list to list for years without correction. It has seemed best to make specific mention of the most noticeable of these errors, but not to do so in the cases with incorrect volume and page numbers only.

Thus, there are references to reports by Ayres and by Quain, many authors considering them separate cases. As a matter of fact, the case was observed by Ayres and was reported by him (*loc. cit.*, No. 3). Later in the same year, Quain reported the case for Ayres at a medical society meeting, and the proceedings appeared in his name (*loc. cit.*, No. 85). Moreover, there is good reason to believe that this specimen was placed in the Museum of the College of Surgeons of England and was described in the Museum Catalogue (*loc. cit.*, No. 135).

There is evidence to show that Pinard and Tarnier saw a case together in 1873 and both reported it. Tarnier's account (*loc. cit.*, No. 100) reads almost exactly like Pinard's (*loc. cit.*, No. 79). The weight of the child, 3590 gm., the successful operation for atresia ani and the peculiar fissure between the esophagus and the trachea point to there having been one case only.

Tarnier (*loc. cit.*, No. 99) reported a case with no unusual features, and Blondeau (*loc. cit.*, No. 5) reported a similar case. From the latter's description it seems certain that it was the same case that Tarnier recorded.

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Bowes' case (*loc. cit.*, No. 8) has resulted in considerable confusion. The title reads, "by C. K. Bowes, Oxon.," and the Germans especially have taken the "Oxon" as the last name of the author, and by corrupting it to "Axon" have given it a place in their literature. Frequent references are made to two cases, Bowes' and Axon's.

Tuck's case (*loc. cit.*, No. 104) has caused even more confusion. Through an uncorrected typographical error, Tuck has been changed to Fuck, and as such is quite generally referred to, particularly by the German authors. Furthermore, English and American bibliographers have accredited the case to Richardson, the secretary of the society before which the case was presented by Tuck.

The specimen in the Dupuytren Museum (*loc. cit.*, No. 18) is said to have been presented by Padieu, who described it in 1835 (*loc. cit.*, No. 74). To further complicate the situation, Cruveilhier (*loc. cit.*, No. 14) describes the same museum specimen. In consequence most authors (Mackenzie, Hoffmann, Kreuter, Happich and Legrand) make this single specimen represent two and sometimes three separate ones.

Houston's specimen (*loc. cit.*, No. 40) was placed in the Museum of the Royal College of Surgeons of Ireland and was described in their catalogue (*loc. cit.*, No. 136). Mackenzie and Hoffman make two cases of this by citing both references.

The two cases reported by Marsh (*loc. cit.*, No. 64) are frequently referred to under the name of Ilott. As a matter of fact, Marsh reported them and they should be in his name.

Weber is the authority for the statement that Spec. No. 395, in the Catalogue of the Museum of the Royal College of Surgeons of England (*loc. cit.*, No. 135), was described by Hirschsprung in 1861 as one of his four cases.

The case of Povis, mentioned by Marsh, Happich and Weber, is the result of a typographical error; the references are to the article by Porro (*loc. cit.*, No. 83).

Viggo-Bendz's report (*loc. cit.*, No. 106) has been the source of some confusion, some authors referring to Viggo, some to Bendz and rarely to both.

Kreuter ascribes three cases to Mondière (*loc. cit.*, No. 67), whereas this author described but two of his own cases and mentioned the recently recorded one of Houston in his article.

The specimen described by Vrolik (*loc. cit.*, No. 111) is undoubtedly the same as that offered by Tilanus (*loc. cit.*, No. 102).

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The reports by Villemin (*loc. cit.*, No. 107), Villemin and Levasseur (*loc. cit.*, No. 108) and by Demoulin (*loc. cit.*, No. 16) all refer to the same case.

The various museum specimens have mostly been described by the individuals who presented them. The two in the Museum of the Boston Society of Medical Improvement and the one in the Army Medical Museum, Washington, D. C., are the only ones that seem not to have been independently described. In the last case, Dr. Lamb, who performed the autopsy, assured me personally of this fact.

In addition to these errors and reduplications, I found many minor mistakes, such as volume, year and page numbers, and have, where possible, corrected them. In some cases I have found the given reference incorrect, but have failed to make the necessary correction. Thus, the report of Melkins, referred to by Weber, Wunsch and others, could not be found after a prolonged search. The same thing is true of the case of Birch-Hirschfeld (Hoffmann, Wittenrood), and of that in the Bibliothek for Laeger (Hoffmann). Wittenrood and Hoffmann refer to a case by Bland-Sutton in the Trans. Path. Soc. London, but give no more data and the case could not be found. Five other reports, those of Hirschsprung, Martin, R. Meier, Rudinger and von der Water, were not available.

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ECTOPIA CORDIS, WITH A REPORT OF A CASE IN A 15-MONTH-OLD INFANT.

By JAMES B. HOLMES, M. D., Baltimore, Md.

(From the Harriet Lane Home and the Department of Pathology of The Johns Hopkins University.)

The term *ectopia cordis* is used to designate a displacement of the heart so that the organ passes out of the thorax, and comes to lie either upon the outer surface of the body or in the abdominal cavity. Three forms are recognized: (1) The *cervical heart,* in which the organ lies high up in the neck; (2) the *pectoral heart* with fissure of the sternum, and (3) the *abdominal heart,* in which the organ has passed through a defect in the diaphragm and into the abdominal cavity. Such anomalies are by no means extremely rare, being encountered in both men and the lower animals. They are found most frequently in prematurely-born fetuses and are often associated with other anomalies.

The anatomist Haller (1706) described one of the cases. Peacock, in 1866, cited 13 cases and described a fourteenth. Ballantyne (1904) mentioned nine additional cases. Another case was described in the same year by Goode. Other American cases are those reported by Holt, Jacobi, Ellis and Welch.

The following case was observed in the service of Dr. Howland in the Harriet Lane Home. The child was first seen in the out-patient department when 7 weeks of age. The family history was negative. There was no history of lues. The child was born at full term and, save that the cord was said to be broken and bleeding, the birth was normal.

Immediately after birth a pulsating mass was noticed in the epigastrium (Fig. 1). This was "raw" and bright red. Soon after birth a scab formed, which came off and was replaced by another smaller scab at each dressing. After four weeks the mass became covered with skin. Cyanosis was not observed in the infant. She developed normally.

At 7 weeks of age the following conditions were noted:

Precordial dulness extends 2.5 cm. to the right of the median line and 2.5 cm. to the left. It extends upward to the 4th interspace. From the upper border of the precordial dulness to the apex of the heart is 6 cm.

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The apex can be felt in the median line 2 cm. above the umbilicus and 5 cm. below the nipple level. The xiphoid process of the sternum is absent; the lower end of the sternum is notched. The action of the heart is regular. The sounds are clearly heard. A loud systolic murmur is heard over the precordium and also over the entire front of the chest.

FIG. 1.—*Photograph of the Patient.*—The tumor mass in the epigastrium is seen emerging from under the costal angle and extending downward almost as far as the umbilicus.

The child was seen from time to time, and the feeding regulated. Her condition remained excellent, but the gain in weight was slow. When nearly 1 year of age she weighed a little over 14 pounds, the birth weight having been 7½ pounds.

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When seen late in the ninth month it was noted that the child occasionally became blue in the face and lips when crying vigorously. Also, that the breath sounds in the right back and axilla were somewhat less intense than in the corresponding areas on the left side, and that

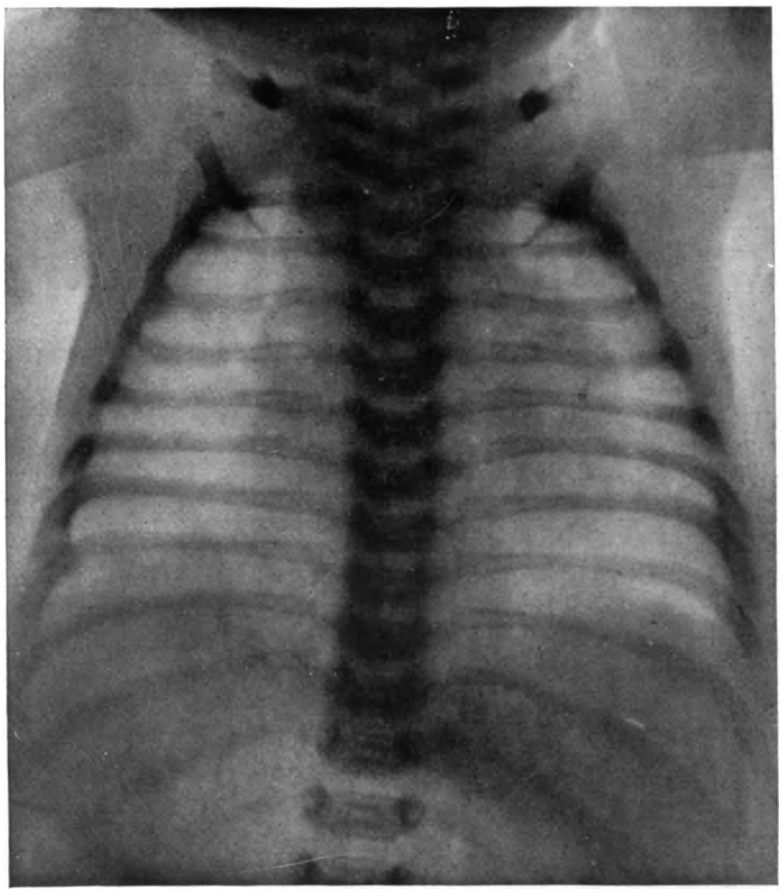

Fig. 2.—*X-ray Photograph of Patient.*—Shows enlargement of the heart to the right and lines suggestive of a defect in the diaphragm.

the left pupil was larger than the right and somewhat irregular in outline.

A fluoroscopic examination (Fig. 2) at this time showed the heart to lie toward the right side and, apparently, entirely above the diaphragm.

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The aorta was in the normal position, as were the stomach and liver. The diaphragm was seen running normally; the left dome appeared to reach a little higher than usual. It was thought that there was probably an extension of the pericardium into the pulsating tumor or sac.

When a little over a year old the child suddenly developed pulmonary symptoms, with fever and convulsions, and was treated at home first for "bronchitis" and then for "pneumonia"; after which the temperature was said to have returned to normal. Two weeks later the child was admitted to the hospital with a temperature of 103.8° F.

On admission, the child, aged 14½ months, presented signs of pneumonia at the left base; later, signs of fluid appeared.

The cardiac findings may be described as follows: There was a defect of the anterior abdominal wall in the epigastric region, about 6 cm. long in the vertical diameter and 4 cm. wide. The xiphoid process of the sternum was absent, and the costal margins were continuous in a gently rounded notch. From this notch, a rounded, vigorously pulsating tumor projected downward in the median line, being about 4 cm. long and 2.5 cm. wide. It could be grasped between the fingers. On percussion there was an area of dulness that was nearly symmetrical in its outlines on either side of the median line, and that extended from the level of the second rib, outward and downward, around and below the area of tumor mass and defect in the abdominal wall. At the second interspaces, the aortic and pulmonic areas, the heart sounds could be heard and were of practically normal relative intensity. Sounds having the character of mitral sounds could be heard about the nipple in the fourth left interspace. A loud systolic murmur was well heard over the whole area of cardiac dulness; it was best heard over the pulsating mass in the abdomen.

Two weeks later thoracentesis yielded a small amount of greenish fluid, from which *Streptococcus hemolyticus* was cultivated. The temperature had been intermittent, ranging from 99° to 102° to 104° F. The child died a few hours later.

Necropsy.—At post-mortem examination the body is seen to be that of a poorly nourished white female infant, 65 cm. in length. The anterior fontanelle is open, admitting three fingertips. There are nine teeth present. The chest and the body generally are well formed. The abdomen is not prominent. There is no clubbing of the fingers.

The sternum measures 6 cm. in length. There is no xiphoid process present. The costal angles and the curves of the costal margins are

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quite normal. Beginning at the lower end of the sternum and extending toward the umbilicus is a hernia-like swelling, 5 cm. in length and about 3 cm. wide. Within the swelling is felt a pear-shaped mass of firm consistence. The mass is somewhat movable, is rounded laterally, bluntly pointed at the lower end and becomes constricted at the upper end as it passes under the costal margins and lower end of the sternum.

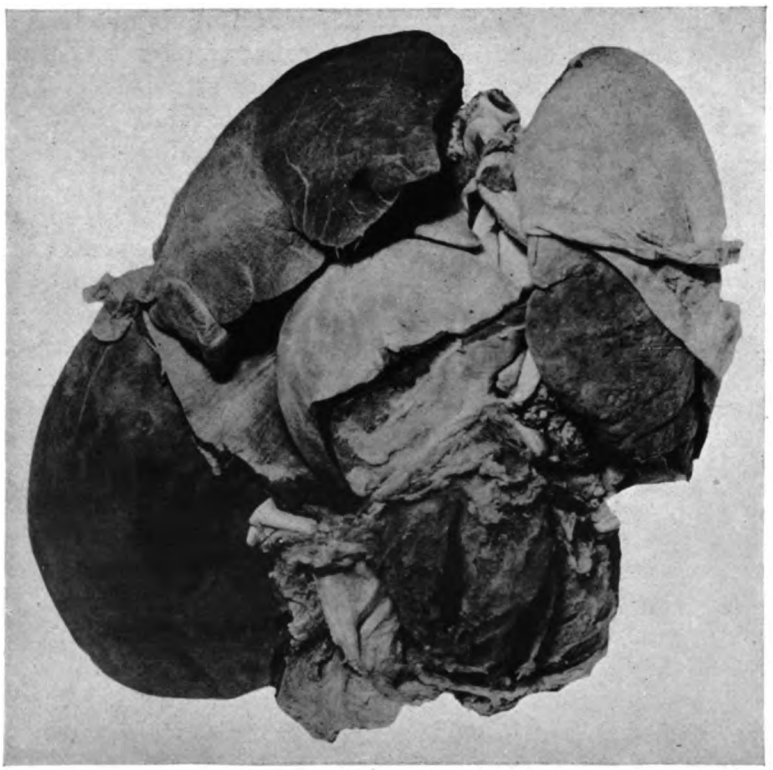

FIG. 3.—***Photograph of Specimen.***—**The right and left ventricles (opened), the tips of the right and left auricles (compare with drawing) and the aorta and pulmonary artery (both slit open) may be seen, as may also portions of the costal cartilages, on the left side in the angle between the left auricle and left ventricle, and on the right side, where the dissection has been made back from the anterior surface of the heart lying against the darker surface of the liver.**

At this point it feels more cartilaginous than in the body of the tumor. The umbilicus is in the normal position. The appearance of the abdomen, apart from the tumor, is quite normal. The genitalia appear normal.

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Only a short incision (15 cm.) is permitted. This is made in the median line over the body of the swelling. The overlying skin, which appears quite normal externally, is bound down to the surface of the tumor, over its anterior aspect, by delicate areolar tissue enclosing small spaces with glistening walls. The largest of these spaces is situated over the anterior aspect of the rounded tip of the tumor, and has a volume of about 1 c. c. None of these spaces contain fluid. A large space is seen to lie under the tumor and to present anteriorly at the median (right) side of the tip of the tumor. Puncture of this admits one to a large endothelium-lined sac that extends upward and backward, and in all ways resembles a large pericardial sac with a downward prolongation behind the tumor mass. The lining of this sac clothes the posterior surface of the tumor and is reflected from it along its lateral margins. Careful dissection of the coverings of the tumor anteriorly shows that a fascial layer may be separated from the under surface of the skin, and that this layer is apparently continuous with the fascia of the large sac or pericardium.

Removal of the sternum reveals a small but meaty thymus, an anterior mediastinum of essentially normal appearance, emphysematous pulmonary lobes on the right side and retracted lobes on the left, where empyema is present. A heart is seen in the normal position (Fig. 3). On opening the pericardial sac in front of the heart the disposition of the various portions of the organ is well seen (Fig. 4). There is a normally placed pulmonary artery and aorta, and a right and left ventricle. What appears to be the anterior coronary artery passes almost straight downward in front. To the right of this lies a somewhat globular mass, resembling a rounded and hypertrophied right ventricle; to the left, a prolongation of this muscular mass extends downward and becomes continuous with the extra-thoracic tumor mass that has already been described. The whole forms an irregularly-shaped heart, the extra-thoracic tumor representing the bulk of the left ventricle.

The displaced portion of the heart lies, as is seen, below the rounded muscular mass that represents the right ventricle, and to the left of it. At the normal position of the apex there is a constriction in the muscular mass. This was perceptible to the palpating finger before section (see above); below this the mass expands to form the extra-thoracic tumor. Just below the point of constriction the pericardium is reflected from the cardiac mass, except along the posterior surface.

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Here it is continued over the surface of the extra-thoracic portion and forms the anterior wall of the downward extra-thoracic prolongation of the pericardial sac, which has already been described. The floor of the pericardial sac is formed by the central tendon of the diaphragm and its radiating muscular fibers. The portion of the diaphragm underlying the extra-thoracic prolongation of the sac is tendinous.

Examination of the diaphragm, as a whole, shows that it is normally placed, normal in its contour and normal in its attachments,

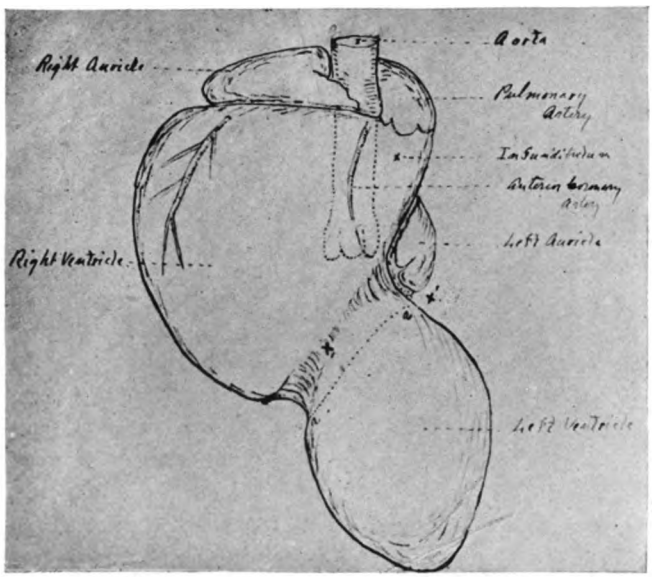

FIG. 4.—*Drawing of Specimen to Show Relation of Parts.* × and ×′ indicate position of nearest (and also adherent) portions of cartilage of costal arch. A-A indicates line of reflection of pericardium from anterior surface of heart. The course and length of the aorta and the position of the sinuses of Valsalva and the aortic cusps are indicated by dotted lines.

except that, symmetrically on the two sides, it leaves the costal margin near the median line and, curving downward, finds its attachment in the fascia of the abdominal wall, as low as 5 cm. below the level of the costal angle.

The relation of the liver, stomach, spleen and other abdominal organs appears quite normal. The round ligament is relatively short.

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Cardiac Cavities.—When the heart is opened by an incision into the rounded mass that appears to represent the right ventricle (Fig. 5) a large chamber is entered. Its walls have the appearance of those of a hypertrophied right ventricle. Into it opens a normally formed but somewhat medially placed tricuspid valve, and a conus arteriosus of normal appearance. This last is continued into a normal pulmonary artery, in which two primary branches and a non-patent ductus Botalli are seen.

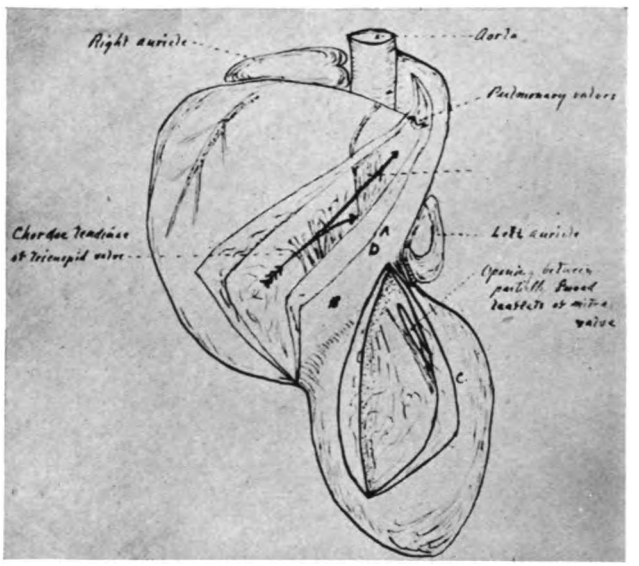

FIG. 5.—*Drawing of Specimen. Right and Left Ventricles Laid Open.*
A.—Level of aortic valves.
B.—Point of origin of anterior papillary bundles.
C.—Point of origin of mitral papillary bundles.
D.—Level of defect in interventricular septum.
Diameter of mitral valve 0.6 cm. Diameter of triscupid valve 2.0 cm. Thickness of right and left ventricular walls respectively, 0.6 and 0.7 cm.

On the median wall of this chamber, the right ventricle, and almost directly opposite to the somewhat medially placed auriculo-ventricular orifice, is a large circular aperture about 1.5 cm. in diameter, through which a blunt probe may be passed downward and laterally into the extra-thoracic tumor mass—a misplaced left ventricle.

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Incision into the aorta shows that it communicates with this second chamber, and that the aperture in the interventricular septum is in the position of the so-called "undefended space." Incision into the left auricle permits the passage of the blunt probe through the mitral orifice into this second chamber, the left ventricle. The mitral valve is normal in form, but the orifice and valve flaps are of abnormally small size. The pulmonary and aortic cusps are normal.

Incision into the right auricle reveals a widely patent foramen ovale. The venous orifices, the Eustachian and Thesbian valves, and the general contour of the cavity appear to be normal.

Closer examination of the chambers of the heart reveals the following additional facts (see Figs. 4 and 5):

The right ventricle is relatively distended and distorted, as well as hypertrophied. Its cavity is enlarged by an out-pouching (dilatation) of the right half of the ventricle. This is shown in the more medial position of the tricuspid orifice, and in the medial (here almost septal) attachment of the great and other papillary muscles of the chordæ tendineæ. The crista supraventricularis is unusually prominent and forms a prominent ridge between the ventricular orifice of the infundibulum and the defect (orifice) in the interventricular septum. The right auriculo-ventricular orifice measures over 2 cm. in diameter.

The right auricle is larger than the left auricle. It communicates with it through the large foramen ovale. The septum of this (septum secundum) is tendinous, redundant and, in the preserved specimen at least, is pouched or deflected or thrown over toward the right side, so as to form a projection into it. The left auriculo-ventricular orifice is quite small, 0.6 cm. in diameter. The tricuspid orifice is over 2 cm. in diameter.

The left ventricle is relatively small. Its walls are of approximately the same thickness as those of the right ventricle. The mitral leaflets are small; their chordæ tendineæ and papillary muscles find their attachment high up on the left ventricular wall. The aortic vestibule is elongated, partly by fusion of the adjacent edges of the mitral leaflets. The apex of the left ventricle is far removed from that of the right ventricle.

The proximal part of the aortic trunk is elongated (see Fig. 5) in such manner as to bring the aortic semilunar valve to a level some centimeters below that of the pulmonary valves. The relation of the sinuses of Valsalva to the aortic cusps is normal, as are apparently the

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origins of the coronary arteries. The prominence of the crista supraventricularis, as seen in examination of the cavity of the right ventricle, is largely due to the close proximity of the underlying aorta.

The pericardial sac contained about 5 c. c. of pericardial fluid of normal gross appearance. (As it is desired to preserve the heart as a museum specimen, further dissection is not made, since it does not seem to promise any important additional information.)

In brief, the findings are: Patent interventricular septum; elongation and downward displacement of the left ventricle; depression of the diaphragm below the level of the costal margin in its attachment near the anterior median line, permitting the displaced ventricle to come in contact with the anterior abdominal wall; downward prolongation of the pericardial sac with deficiency (early adhesions?) over the anterior aspect of the left ventricle and substitution of the multiple pericardial sac-like spaces; hernial protrusion of the abdominal wall in the epigastric region; empyema.

Character of the Circulation.—In considering the character of the circulation in the heart just described, certain facts seem to be of especial importance. Among these are the following:

The left ventricle is relatively small, and to a considerable degree is detached from the main body of the heart. The mitral orifice is small, so small as to suggest that it played a less than normal part in the transmission of blood from the left auricle (pulmonary circulation) to the systemic circulation. The walls of the left auricle are not especially hypertrophied. There are features about the septum and appearance of the foramen ovale that may indicate that the foramen served for the passage of blood from the *left* to the *right* auricle. The right auricle and right ventricle and the passage between them are relatively very large. Finally, the defect in the interventricular septum is so placed that during systole of the ventricles blood from the right ventricle would appear to pass with about equal facility into the conus arteriosus (infundibulum) or into the aortic vestibule. It is into the latter, and not into the displaced left ventricle cavity, that the septal foramen opens. In the aortic vestibule, blood coming from the right auricle through the interventricular septal foramen would meet and mingle with blood from the left auricle, by way of the mitral orifice, coming under similar pressure from the left ventricle. Thus the deficiency in size of the left ventricle would be compensated for by the assistance of the right ventricle.

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Of published cases the one most resembling the above is that recorded by Holt in 1897. The conditions in his case were briefly as follows: The patient, a boy, presented immediately upon birth an abdominal tumor the size of a goose's egg, only partly covered by normal skin (Fig. 6). This was evidently in greater part an ordinary umbilical hernia, but in it there was a small, hard, pulsating body. The

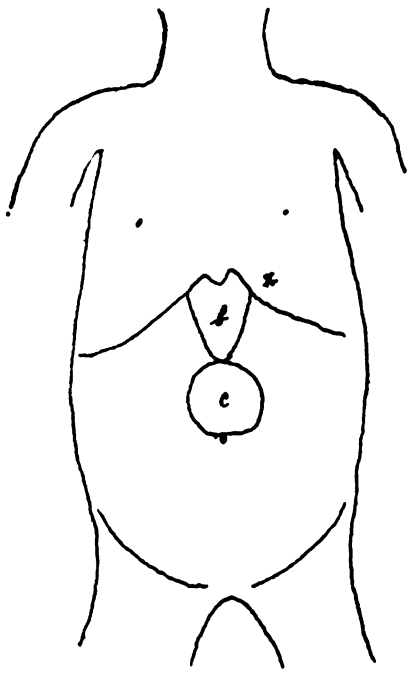

FIG. 6.—Diagram showing the conditions in Holt's case, a healthy 5-months-old boy.

X indicates the point where the murmur was loudest; *b* indicates the heart; *c*, the area where the skin was undeveloped.

hernia was easily kept reduced with an abdominal pad, and the child developed normally. There was severe, almost constant cyanosis in the early weeks, but this gradually lessened until at 5 months it was apparent only on exertion. A loud systolic murmur was present.

The cyanosis and loud systolic murmur were believed to be due to pulmonic stenosis. The prognosis for life appeared good.

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The clinical picture as described at 5 months of age was as follows:

The recti muscles of the abdomen were widely separated. In the median line was a circular area, about two inches in diameter, where normal integument was wanting, and where only a thin membrane covered the umbilicus. This surface resembled that often seen over a spina bifida. When the pad was removed the hernial protrusion became about the size of half an orange. In the epigastric region in the median line, extending from the ensiform cartilage into the upper part of the area previously mentioned, was a pulsating tumor of conical shape, one and one-fourth inches broad at its base, which was the ensiform cartilage, and two inches in length. It was covered only by integument and subcutaneous tissue, the muscles being separated at this point fully an inch. The body was evidently the heart. Through the thin coverings all the cardiac movements could be easily observed, diastole and systole being almost as well defined as in an animal when the chest is opened. By placing the tips of the fingers beneath the apex, the heart could be lifted until the apex was at the ensiform. This movement did not seem to cause the child the slightest disturbance. A loud systolic murmur was present and could be heard in front all over the chest. It was most distinct a little to the left of the ensiform cartilage. It was not distinct behind. A respiratory murmur was present anteriorly over the whole chest, even in the area usually occupied by the heart, but was not very loud. There was moderate clubbing of the fingers. Examination of the abdomen and chest chamber disclosed nothing abnormal.

The diagram accompanying the description shows yet more clearly the resemblance of Dr. Holt's case to the present one.

Discussion of the Anomaly.—Ectopia cordis is recognized as being due to some defect in the closure of the walls of the body of the embryo in the mid-line. At first spread out like a disc, the edges of the body appear gradually to curl inward and fuse along their margins, closing last in the neighborhood of the umbilical cord. Hernial defects at this point are very common in the newly-born. The defect may be of greater or less extent. It may involve the thoracic region, in which case the heart is likely to protrude in some measure. MacMurrich notes that Hiss has observed ectopia cordis in a 15 mm. embryo. Or it may extend from the episternal notch to the umbilicus and permit extrusion of other viscera besides the heart—a condition better classified as *gastroschisis* (Ballantyne).

Such conditions are doubtless not uncommon among embryos that fail to develop. Some have thought they are due to adhesions in the fetal membranes. In fetuses born at or near term, cervical or thoracic hearts are the more common forms of ectopia cordis. Cervical hearts

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have proved incompatible with life. Infants born with thoracic hearts may live for days. The pericardium is usually deficient in the parietal layer and the heart is exposed. In Goode's case (the child died on the sixteenth day), the surface was oiled several times daily and protected from contact with clothing. Ellis cites a case (Lannelongue's) in which the thin membrane covering the heart sloughed on the fifteenth day, and the skin margins were successfully united over the heart with sutures.

Instances of abdominal heart appear to be much less common.* The condition appears to be more compatible with life. In Deschamp's case, an abdominal heart was found in a healthy soldier. At autopsy the heart was found to occupy the position of the left kidney in the lumbar region, and the vessels passed into the thorax through an opening in the diaphragm. Holt thought that in his case there must have been a congenital defect in the diaphragm, "as a result of which instead of the usual one of the protrusion of the abdominal contents into the thorax, the heart had become displaced downward. This had doubtless been favored by the imperfect development of the abdominal walls which also led to the umbilical hernia." Post-mortem confirmation of this view is lacking.

In the present instance the diaphragm appears to be intact. It is abnormal merely in its point of attachment anteriorly. Whether this is the result of the cardiac anomaly, or the cause of it, is a difficult matter to determine. The heart, as is well known, is formed high in the cervical region, and so, too, is the diaphragm. Both are drawn (or forced) progressively downward during the growth of the embryo and come to occupy their adult position. In the present case, a portion of both descended to a lower level than usual. The position of the umbilicus was not abnormal, and there was no umbilical hernia; nor were there any anomalies noted elsewhere in the body.

It does not seem possible to determine in the present instances at what stage in development of the heart abnormal forces were brought to bear upon it, resulting in malformation. The answers to the questions here raised will doubtless be found in the study of embryos with defects in the closure of the body walls.

*** It is not clear that either of the cases here described is properly to be classified as such, if by abdominal heart is meant strictly one that, in whole or part, has escaped through some defect in the diaphragm into the abdominal cavity.**

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STUDIES IN THE MECHANISM OF ABSORPTION FROM THE COLON.*

By SAMUEL GOLDSCHMIDT and A. B. DAYTON.

(From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins University, Baltimore, Md.)

The factors of diffusion and osmosis in the mechanism of absorption from the intestinal tract have received much attention. Although it has been conceded that these factors do play a part in the process, it is held by most of the former investigators that a "vital factor" is interposed.

A point of support for this hypothesis has been the "irreciprocal" character of the membrane; a property which has no analogue in any known physical system. To be sure, small quantities of diffusible blood constituents have been demonstrated in the intestinal test fluids, but the amounts have been so small that they have been supposed to have their origin in the excretions or secretions of the intestine, independent of physical processes.

The work I wish to report is an attempt to separate the physical from the so-called "vital" factor.

The colon of the dog has been chosen for this investigation. By our experimental methods it has been possible to introduce and remove fluids with a considerable degree of quantitative accuracy.

For the present discussion the behavior of sodium chloride in various concentrations and distilled water will be presented.

When sodium chloride solutions of concentrations above 1.2 per cent are introduced into the colon, the following changes in volume are noted: At first the volume of the colonic contents increases, the increase being followed after a given point by a diminution in volume. For convenience of reference we have called this point the "crest" of the volume wave on the introduction of strong sodium chloride solutions. If allowed to remain in the colon, the whole volume of solution will gradually be absorbed.

* Abstract of a paper presented before The Society of Biological Chemists, New York, December, 1916.

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Coincidently with this increase of volume, as is to be expected, the concentration of chlorides is diminished; the total chlorides present are decreased, which indicates that chlorides have passed across the membrane towards the blood, while water was passing in the opposite direction. The subsequent observations upon the concentration of chlorides give decreasing values, finally coming to a point which shows little change.

The osmotic pressure of the colon contents, as represented by Δ, the depression of the freezing point, shows a persistent diminution. The values for Δ observed compared with the values obtained from solutions of sodium chloride of equal concentration show an immediate divergence which continues in spite of the constant decrease of chlorides in the colonic contents. We have interpreted this difference as due to "other substances" passing into the colonic contents, in an attempt to maintain partial pressure equilibrium of the diffusible substances on either side of the membrane.

A point of interest in the above process is the fact that the concentration of chlorides and the Δ of our "crest" is always at a point which varies but slightly in normal animals. However, increased concentrations of chlorides in the blood, by intravenous infusion, cause an increase of the concentration of chlorides and the Δ of the "crest."

If solutions of sodium chloride below 0.6 per cent are introduced into the colon, the volume diminishes progressively, but the concentration of chlorides increases. The latter finally comes to an equilibrium between 0.6 and 0.7 per cent, or at the level of the chlorides in the blood.

The Δ of the colonic contents increases progressively, tending to simulate the blood Δ. Here also the Δ observed and that of equal sodium chloride concentrations show a difference. Increase of chlorides in the blood by intravenous infusion causes a readjustment of this point of equilibrium of chloride concentration between the colonic contents and the blood.

When sodium chloride solutions below 0.2 per cent concentration or distilled water are introduced into the colon, the volume is less at each successive period of observation. The concentration of chlorides increases as does also the Δ of the colonic contents. The total amount of chlorides present in the contents increases up to a concentration of from 0.12 to 0.17 per cent; at this point the total chlorides present in the colonic contents begin to fall, in spite of the fact that the concentration is rising. This concentration between 0.12 and 0.17 per cent

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we have called our "low point." This phenomenon may explain the unsuccessful efforts to demonstrate large amounts of chlorides in the intestinal contents which have led to the application of the term "irreciprocal" to the membrane of the intestine. If fresh portions of distilled water are introduced into the colon and removed after a short interval, it is possible to rob the blood of a large amount of chlorides. An increase of available chlorides in the blood by intravenous infusion causes an increase in the amount of chlorides passing into the colonic contents.

Towards solutions of sodium chloride the colon acts essentially like a permeable membrane; both solvent and solute are allowed to pass; there is an attempt at partial pressure equilibrium of diffusible substances between the colonic contents and the blood. The great constancy of the process is, no doubt, due to the constant conditions under which it takes place in the normal organism. It has been shown that changes beyond the normal of but one factor, namely, sodium chloride, on the blood side of the membrane affect the mechanism. The number of factors involved are numerous and of a complicated order in the intact animal. The process is dependent upon the life of the membrane, or upon a "vital" factor, to the extent that conditions for the proper performance of the processes involved be maintained. Obviously, damage to the membrane or interference with the normal conditions on the blood side would cause a disturbance in the mechanism.

A more minute study of this phase of our problem is now in progress.

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REPORT OF TWO FATAL CASES FOLLOWING PERCY'S LOW HEAT TREATMENT OF CARCINOMA OF THE UTERUS.

By V. N. LEONARD and A. B. DAYTON.

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In 1912, in a series of articles, J. F. Percy advocated the application of long-continued low heat in the treatment of otherwise inoperable carcinoma of the uterus. This procedure is based upon a principle claimed by Percy, that carcinoma cells are killed by low penetrating heat insufficient to destroy normal tissue. He introduces an electric heating iron into the uterus and maintains for a considerable time a temperature insufficient to char the tissues.

As far as has been ascertainable, the only reported untoward results with the Percy method are a brief mention by Percy of infection and fistula formation, and the one instance of death from sepsis reported by Boldt.

For this reason the following cases treated by this method in the Gynecological Clinic of The Johns Hopkins Hospital with fatal results, are reported.

CASE I.

CLINICAL HISTORY.—L. D., a white woman, aged 52, was admitted to the hospital, April 24, 1916. Examination showed an inoperable carcinoma of the cervix of the uterus.

The Percy method was therefore used and the low heat applied for one-half hour in each broad ligament.

Her post-operative course was marked by a slight amount of shock immediately following the operation but on the second and third days the abdomen was distended and she vomited large quantities of a brown watery fluid. There was involuntary loss of urine. The temperature never went above 100° F. On the fourth day the abdominal distension was more marked, her condition became worse and as preparations for an enterostomy were being made she died suddenly with symptoms which suggested pulmonary embolism.

AUTOPSY No. 4674 (17 hours after death). Abstract of protocol.—The body is that of a well-nourished white female, 152 cm. in length. The abdomen is distended. A clean mid-line incision is held together by sutures.

The *peritoneal cavity* contains 100 c. c. of serosanguineous fluid which contains some flakes of fibrin. The large and small intestine are distended

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down to the sigmoid, which is collapsed. They are glued together in places by fibrinous exudate.

Both *pleural cavities* contain about 500 c. c. each of a clear blood-tinged fluid. The pleural surfaces are everywhere smooth and glistening.

The *pericardial cavity* contains 15 c. c. of clear yellow fluid but is otherwise normal.

The viscera show extreme cloudy swelling.

The *lungs* are congested and in one of the main branches of the right pulmonary artery is an embolus coiled several times upon itself. The smaller branches are nearly all thrombosed, as are also some of those in the left lung.

The stomach and duodenum are distended with gas. There are about 24 round ulcers from 1 to 7 mm. in diameter scattered over the mucous surface of the stomach but more numerous at the pyloric end. They have clean bases and edges which are not elevated. The loss of substance apparently extends to the muscularis. The peritoneal surface shows nothing abnormal. The mucosa aside from the ulcers is smooth and pale. The duodenal mucosa is intact.

The pelvic organs are removed in one mass. The *rectum* and *sigmoid* show no gross abnormalities. No anatomical obstruction can be found. They are removed readily from the remaining pelvic organs. Externally the uterus is normal in size and contour. The peritoneum over the bases of the broad ligaments is discolored a purplish red. The vesico-vaginal space is obliterated and the posterior wall of the bladder is closely adherent to the vagina. The *ureters* show nothing abnormal down to their entrance into the broad ligament. The mucous membrane of the *bladder* is injected except in the trigonum where there is a fistula, measuring 2 x 3 cm., opening into the vagina. The edges of the fistula are reddish black and necrotic in appearance. A probe passed through the proximal end of the left ureter emerges in the wall of the fistula; passed through the right ureter it stops in a necrotic mass about 3 cm. from the wall of the bladder.

In the vagina the orifice of the fistula is similar to that described in the bladder. The cervix and the tissues directly surrounding it are destroyed. The tissues in the neighborhood are no longer recognizable. They have a foul odor, a greyish-white color and a putty-like consistence. On section this necrotic mass ends abruptly about 1 cm. from the necrotic surface. Beyond this here and there in the bases of the broad ligaments there is a gritty material of cartilaginous consistence.

In the *microscopic examination* of the viscera the following abnormalities were noted:

Lungs.—The alveoli particularly in the sections from the posterior portions contain a few red blood cells.

Stomach.—The gastric mucosa is well preserved. As an ulcer is approached the definition of the cells of the mucosa becomes obscured and the nuclei are unstained by hematoxylin. The loss of substance extends through the submucosa to the muscularis. At the inner edge of the muscularis there is a distinct line of polymorphonuclear cells which form

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the base of the ulcer (Fig. 1). A large blood-vessel in the immediate neighborhood of the ulcer is intact.

Liver.—In the central part of the lobule the cells show fatty change. Elsewhere they have undergone extreme swelling and disintegration.

Kidneys.—The general structure is normal. There is extensive epithelial necrosis in the convoluted tubules.

The *lymph glands* are normal. They do not show necrosis or metastases.

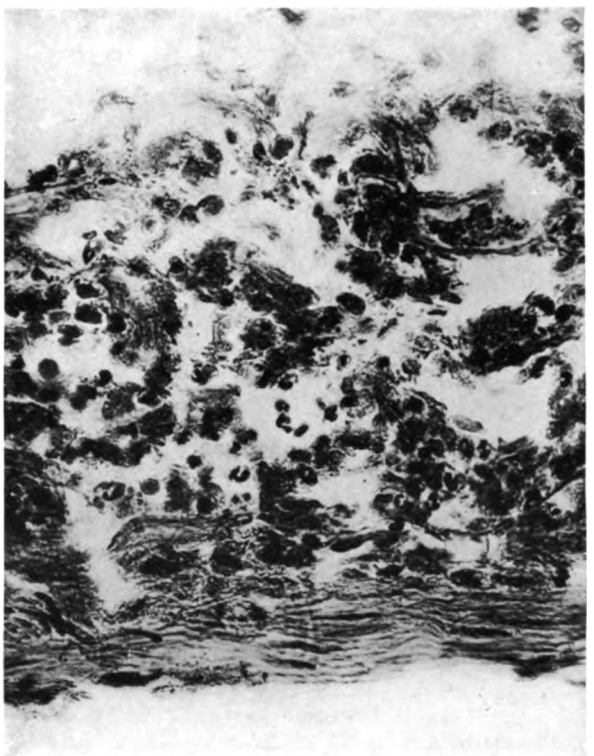

FIG. 1.—Base of gastric ulcer showing polymorphonuclear cells.

Brain.—There is a moderate grade of satellitosis. No other change is noted.

Pelvic Organs.—Sections from both broad ligament and from the posterior wall of the vaginal vault at the level of the cervix show perfectly preserved squamous-cell carcinoma (Fig. 2). Sections from the necrotic areas stain a uniform bluish pink and carcinomatous tissue can be distinguished only by its outline. All gradations can be seen between this necrotic area and

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the surrounding well-preserved tissue (Fig. 3). In these intermediate areas many of the nuclei of the cells are unstained and show karyolysis or karyorrhexis. Other cells intermingled in these areas have bright-pink-staining cytoplasm and a sharp well-stained nucleus. Many mitoses are seen. The changes observed in the connective tissue and smooth muscle of the pelvis are analogous to those in the neoplastic tissue. The nuclei

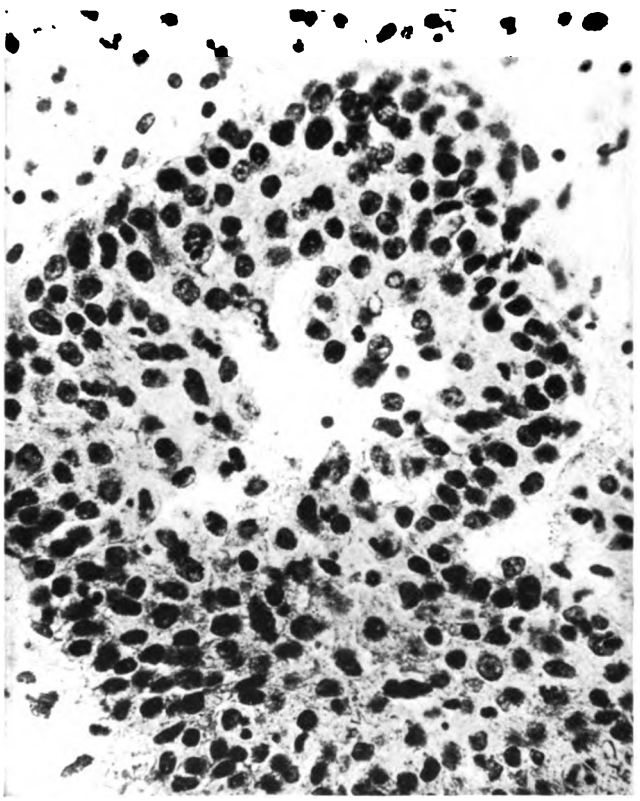

FIG. 2.—Carcinoma cells in Case I. (High power.)

become obscured and broken up and the tissue stains uniformly bluish pink. The vessels are all thrombosed. Masses of polymorphonuclear cells occur throughout the tissue as well as large blue-staining amorphous masses of bacteria. There are several areas where carcinoma cells are invading normal tissue. In these there is nothing to indicate any difference in susceptibility between them; the cytological changes are in every instance equidistant from the necrotic edge. In making blocks care was taken to cut them in a plane radial to the necrotic edge to make the observations

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certain. In a block taken posteriorly from the cervical region the zone of cytological change had a maximum width of 6 mm.

ANATOMICAL DIAGNOSIS: *Primary.*—Carcinoma of the cervix of the uterus; (operation; laparotomy and cauterization); vesico-vaginal fistula; intestinal distention; thrombosis of pelvic veins; pulmonary embolus;

FIG. 3.—Coagulated tissue containing remains of carcinoma below, normal tissue above.

hydrothorax (bilateral); multiple gastric ulcers; epithelial necrosis of kidneys; cloudy swelling of viscera.

***Subsidiary.*—Chronic mitral endocarditis; fatty liver; encapsulated caseous tuberculous bronchial lymphadenitis.**

The pathological changes in this case—hemorrhagic serous effusions, extreme cloudy swelling of the viscera, renal epithelial necrosis and gastric ulcers—correspond to the findings in extensive superficial burns.

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It is therefore possible that death may, in part, be due to the same unknown factors. On the other hand, the pulmonary embolism was important in the sudden death.

CASE II.

CLINICAL HISTORY.—I. P., a white woman, aged 55 years, was admitted to the hospital for the first time in October, 1915. Examination showed early carcinoma of the cervix. She was operated upon and the uterus removed with a wide margin of parametrium on both sides.

Five months later, on April 26th, she was again admitted to the hospital and a firm adherent mass, 5 cm. in diameter, was found in the left broad ligament.

At the operation the heating point was introduced into this mass till its tip came within 1 cm. of the peritoneal surface, and heat which was just insufficient to char the tissue was maintained for two hours.

At the conclusion of the operation the patient was in excellent condition. The pulse had varied from 100 to 120 throughout.

Post-operative course. The patient's condition for four days was excellent. On the fifth day urinary incontinence developed. Her temperature varied between the extremes of 100° and 102.5° F. but on the tenth day it rose to 105° and remained irregularly elevated reaching a maximum of 108°. Blood cultures on the twelfth and fourteenth days showed respectively 10 and 150 colonies of streptococci per cubic centimeter. Death occurred on the sixteenth day.

AUTOPSY No. 4687.—Six hours after death. (Abstract of protocol.) The body is that of a poorly-nourished white woman 157 cm. in length.

A recent mid-line scar, in perfect condition, runs from the umbilicus to the pubis. There are a few delicate fibrinous adhesions in the pelvis and there is a little pocket posterior to the left broad ligament containing 3-4 c. c. of green pus.

The *left pleural cavity* is normal.

The *right pleural cavity* contains 500 c. c. of clear yellow fluid showing flecks of fibrin. A little fibrin can be seen on the surface. The pericardial cavity contains 50 c. c. of a cloudy yellow fluid. Smears show many polymorphonuclear leucocytes and long chains of streptococci. There are many extensive subserous ecchymoses in the pericardium.

The viscera are normal except for cloudy swelling.

The *pelvic organs* are removed in one mass. The rectum and sigmoid show no gross abnormality and are readily removed from the remaining organs. The peritoneum over the vaginal vault after the first operation has closed perfectly. It is injected and there is a slight fibrinous exudate. The vesico-vaginal space is obliterated and the bladder is closely adherent to the vagina. The ureters are normal up to their entrance into the broad ligament. The mucous membrane of the bladder is injected. In the trigonum there is a fistula, less than 1 cm. in diameter and with black necrotic edges, which passes from the vagina and bladder. A probe passed

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down the right ureter emerges at the edge of the fistula; passed down the left ureter, it stops in a necrotic mass about 2 cm. from the wall of the bladder.

In the vagina the edges of the fistula are much more discolored than in the bladder. The vaginal vault is intact but extending out into the base of the left broad ligament is a soft, grey, necrotic mass with a central

FIG. 4.—Blue zone separating coagulated tissue above from normal tissue below.

opening representing the position of the coagulating point. Within 1 cm. of this lumen the necrotic tissue ends abruptly in normal-looking fat and connective tissue.

Microscopically, the viscera show no particular change.

The *pelvic tissues* are very edematous and polymorphonuclear cells are prevalent everywhere. The smaller blood-vessels are thrombosed. Peripheral to the area of necrosis there is a zone, with a maximal width of

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not over 6 mm. in any section, where the tissue is uniformly pink-staining except for blue amorphous masses of bacteria. The tissue structure in this area has entirely disappeared. Separating this zone of coagulation from the more remote tissue is a zone, about 1 cm. in width, which stains a deep blue and under the high power is seen to consist of granular nuclear material and polymorphonuclear cells (Fig. 4).

FIG. 5.—Carcinoma cells. Case II.

Carcinoma cells can be found only in the left broad ligament near the bladder sinus. They are situated in clumps just beyond the zone of coagulation (Fig. 5).

ANATOMICAL DIAGNOSIS: *Primary.*—(1) Previous panhysterectomy for carcinoma of the cervix, (2) recent ineffectual cauterization for recurrence in the left broad ligament; streptococcus septicæmia; purulent pericarditis; fibrino-purulent pleurisy (left).

Subsidiary.—Pulmonary congestion. Encapsulated apical pulmonary tuberculosis.

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Summary.

The primary effect of the Percy cautery is a necrosis, which extends more or less uniformly in all directions from the coagulation point.

A mass of sloughing coagulated tissue of this type offers an ideal medium for the growth of microorganisms. This view is borne out by the sections from these two cases. It probably will be found impossible to prevent infection of this area, and, once infected, the thrombosed vessels of the region may offer a ready entrance for the microorganisms into the general circulation. Hence the danger of septicæmia is considerable.

It seems most probable that experiences similar to those recorded above must have been frequent wherever this method has been used extensively, yet there is, as far as we have been able to find, only one complete report of a fatal case in the literature, that of Dr. Boldt. This case is of particular interest because the findings agree in all essential points with those in Case II, and emphasizes the probable frequency of the development of septicæmia from the infected area.

In an article in the Pennsylvania Medical Journal (January, 1916), Percy mentions four cases in which post-mortem examination disclosed "more or less of these lytic cells in a pultaceous mass, free in the pelvis." In one case, "there was easily a pint of this material." The description of the clinical picture of these cases agrees fairly well with that of a fatal septicæmia and it seems possible to suppose, since neither blood cultures, microscopical examination nor cultures of the mass were reported, that the four cases may have been complicated by sepsis.

In Dr. Boldt's case, and in the two cases reported above, the Percy technique was applied most rigidly; nevertheless, microscopic sections show actively growing uninjured local carcinoma 16 days afterward. In both of our cases it was found within 1 cm. of the previous site of the heating iron.

Conclusions.

1. The prolonged treatment of large carcinomatous masses by low heat may be rapidly fatal and associated with general changes throughout the body, similar to those observed in cases of fatal cutaneous burns.

2. The necrotic mass produced by the cautery forms a particularly favorable medium for bacterial growth. The organism may spread to the surrounding tissues or reach the general circulation through the

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local thrombosed vessels. It seems probable that the greatest danger in the application of the Percy cautery is the local infection and a subsequent general sepsis.

3. Finally, there is no evidence from these two cases that carcinoma is more susceptible to heat than is normal tissue. Moreover, it would appear that the procedure is ineffectual in eradicating the carcinoma.

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THE RELATIONSHIP IN TYPHOID FEVER BETWEEN SPLENIC INFARCTS AND PERITONITIS UNASSOCIATED WITH INTESTINAL PERFORATION.

By A. B. DAYTON.

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Especially in the French literature cryptogenetic splenic infarcts, not uncommonly found in cases of fatal typhoid fever, have been suggested as the possible cause of a peritonitis, when it is unassociated with any demonstrable perforation of the intestine. This hypothesis seems reasonable because the bacilli are present in great numbers in the splenic tissue, so that, when this undergoes coagulative necrosis, complicated frequently by subsequent softening and usually by a localized acute perisplenitis, the bacilli may find a ready access to the peritoneal cavity.

Yates who collected much evidence concluded that while the peritonitis may be hematogenous in origin, or result from the migration of bacteria through an intestinal wall, made abnormal by meteorism, for example, it usually is caused by extension through the bases of deep intestinal ulcers. Evidence to support this contention is offered by him in experiments in which emboli composed of agglutinated red blood cells have induced lesions in the intestinal walls and so favored transmission to the peritoneal cavity. The case reported below directed our attention to this subject:

Clinical History.—The patient, a colored man, aged 27, entered The Johns Hopkins Hospital in the service of Dr. Theodore Janeway, September 14, 1915, on the seventh day after the onset of symptoms. Abdominal pain and tenderness had been present from the beginning.

While in the hospital he had several internal hemorrhages, one of about 750 c. c. His general condition gradually became worse until October 1st, the twenty-third day of the disease, when the symptoms and signs of perforation developed.

At operation a "considerable amount" of cloudy yellowish fluid was found in the peritoneal cavity but no gas. Cultures of the fluid showed uncontaminated *B. typhosus*. The peritoneum of the ileum just above the cecum was red and edematous. A loop of the bowel was brought to the abdominal wall and an enterostomy performed in two stages. The con-

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dition of the patient gradually became worse and he died four days later on the twenty-seventh day of the disease.

AUTOPSY No. 4469. Two days after death. (Abstract of protocol.) The body is that of a very emaciated young colored man, 166 cm. in length. In the lower right rectus region there is a recent surgical incision that has healed by first intention except at the lower end which is open for about 2 cm. and through which fecal fluid has been discharged.

There is no free gas in the peritoneal cavity. It contains about 500 c. c. of clear serosanguineous fluid. An enterostomy 10 cm. above the ileocecal valve communicates with the external sinus. The peritoneum is everywhere smooth and glistening except just below the wound where about 75 cm. of the lower ileum are matted together by a fibrinous exudate. There are no pus pockets. The abdominal lymph glands are enlarged, especially the mesenteric. The thoracic cavity is normal.

The *heart* weighs 210 gm. and is normal.

The *lungs* are congested and show throughout diffusely scattered raised dry areas of bronchopneumonia.

The *spleen* weighs 350 gm. and measures 14 x 10 x 5 cm. It is soft except for three large white firm areas; the largest measures 3 x 4 cm. and the smallest 1.5 cm. in diameter. Over these there is a thick fibrinous exudate. The other viscera are normal except for cloudy swelling.

The *intestines* have undergone considerable post-mortem change. The serous surface of the lower 100 cm. of the ileum is injected and through it the enlarged Peyer's patches are seen. This part of the intestine was matted together by purulent fibrinous adhesions around the enterostomy wound. The mass was pulled apart and the gut opened and although it was carefully looked for no perforation could be found. There are a series of enlarged swollen lymph follicles in all stages of sloughing and ulceration in the lower ileum especially around the ileocecal valve. One of these ulcers included in the adherent mass of intestines shows at its base a pin-point opening through which gas can be made to bubble. Around this minute orifice the tissue is gray and necrotic. Three enlarged ulcerating follicles are found in the ascending and transverse colon.

MICROSCOPICAL NOTES.—The splenic pulp shows the usual picture found in typhoid fever. The light firm areas are typical fresh infarcts.

In the section of the intestine the picture is obscured by post-mortem changes.

The other organs show nothing of importance.

ANATOMICAL DIAGNOSIS: *Primary.—Typhoid fever;* splenic infarcts; acute fibrinous perisplenitis; typhoid peritonitis. (Operation: Exploratory laparotomy.) Perforation of typhoid ulcer of ileum; localized fibrinopurulent peritonitis.

Subsidiary.—Bronchopneumonia.

This case gave all the clinical indications of peritonitis following perforation. The patient was operated upon with the expectation of finding a perforation, but careful search failed to show any. A peri-

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tonitis, however, was found, as is proved by the excess and character of the fluid and by the pure culture of *B. typhosus* which was obtained.

In the first 4000 autopsies in The Johns Hopkins Hospital there were 166 cases of typhoid. Of this number 53 (31.9 per cent) were complicated by perforation and peritonitis; 110 (63.3 per cent) were without either perforation or peritonitis. The remaining three (1.8 per cent) had definite peritonitis but no perforation. From one of these a pure culture of *B. typhosus* was obtained from the peritoneum. In another, *B. typhosus* was obtained together with an unidentified white micrococcus. In these three cases of peritonitis in each instance there were splenic infarcts. There were seven other instances of splenic infarcts without peritonitis.

That the three cases of peritonitis without perforation occurred in the 10 cases of splenic infarct without a single case in the 103 cases uncomplicated by either perforation or splenic infarct together with the reported case, is important presumptive evidence that peritonitis without perforation is probably due to the splenic infarct.

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LEFT DUODENAL HERNIA. REPORT OF A CASE.

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Duodenal hernias are divided into two groups, right and left, determined by their extension from the median line. A typical example of the former is reported below.

CLINICAL HISTORY.—S. W., white, male, aged 50 years, entered The Johns Hopkins Hospital, April 1, 1916, suffering from a pulmonary affection from which he died nine days later. In the routine examination the patient stated that he had never had any gastro-intestinal symptoms, and while he was in the hospital none were observed. In the physical examination the abdomen was described as "scaphoid." The edge of the liver was felt in the epigastric notch but no other tumor mass was noticed.

AUTOPSY No. 4646. (Abstract of protocol.) The hernia is entirely independent of the pulmonary tuberculosis from which the patient died and the description will be confined to the former.

The abdomen is slightly sunken. Its form is otherwise normal. There is about 1 cm. of subcutaneous fat. The peritoneal cavity contains no fluid and its surfaces are smooth and glistening. A large fatty omentum hangs down over the intestines and is adherent by a few delicate fibrous adhesions in both inguinal regions. When the omentum is turned back, the entire small intestine is found enclosed in a large cyst-like structure which measures about 25 cm. in its largest diameter and 20 cm. at the base. The other abdominal viscera are normally disposed. (Further examination showed them to be normal.)

The entire small intestine can be seen enclosed in the thin transparent sac. It is made up of an inner and outer layer of peritoneum. The outer layer is continuous with the mesocolon and parietal peritoneum. It has an orifice posteriorly, just to the right of the mid-line at the level of the third lumbar vertebra. The orifice is oval in shape with its axis in a longitudinal position. It measures 3 x 2.5 cm. and just admits three fingers. Its anterior edge consists of a cord-like thickening. From this opening the ileum which immediately joints the cœcum emerges so that no small intestine is exposed. The intestine can be pulled out of the sac almost entirely. The last few feet are withheld only by the tautness of the mesentery. The intestine enters the sac at the duodenojejunal junction from a retroperitoneal position posterior to the sac, so that it is hidden from view. At no point is there any constriction of the intestine or any evidence of interference in function.

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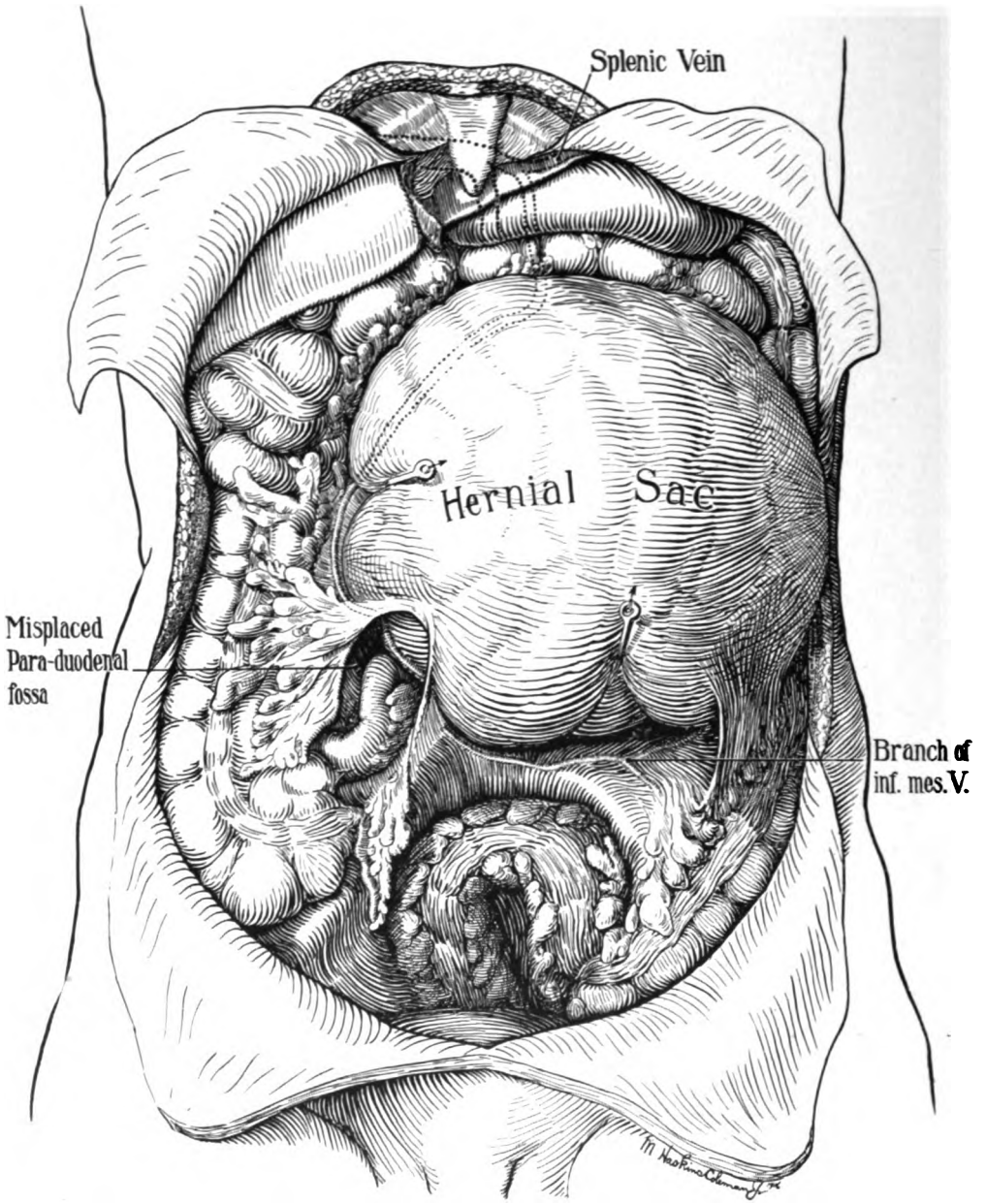

FIG. 1.—Drawing of the dissection showing the relationship of the inferior mesenteric vein to the hernia.

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Fig. 2.—Photograph of the normal peritoneal cavity of a child showing the inferior mesenteric vein and behind it the paraduodenal fossa.

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The various blood-vessels in the vicinity of the sac are all normal except the inferior mesenteric vein. The venous supply of the descending colon and part of the sigmoid is entirely through large anastomoses with the branches of the superior mesenteric vein from the transverse colon. A branch of one of the veins from the descending colon extends backwards behind the hernial sac at the point where the peritoneum of the sac is reflected over the sacral prominence. It soon loses its lumen and becomes a cord not over 1 mm. in thickness. This is traced around over the orifice, where it lies in the anterior lip, then upwards through the transverse mesocolon and finally ends in the splenic vein. About 5 cm. from its junction with the splenic vein it again acquires a lumen (Fig. 1).

This cord is the obstructed inferior mesenteric vein and it proves that the condition is a hernia into the fossa that is formed by the fold of peritoneum which the inferior mesenteric vein raises up as it arches over from its origin in the splenic vein on its way to the descending colon (Fig. 2). This is called the paraduodenal fossa or the fossa of Landzert. Mr. Moynihan believes that all duodenal herniæ develop from this sac and that Treitz's hernia was also of this nature. This case supports his view.

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HISTOLOGICAL AS RELATED TO PHYSIOLOGICAL AND CHEMICAL DIFFERENCES IN CERTAIN MUSCLES OF THE CAT.*

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The object of this paper is to call attention to some morphological differences between certain muscles of the cat, which are believed to correspond to a number of the physiological and chemical differences in the same muscles as set forth by Lee, Guenther, Meleney, Scott and Colvin in a series of interesting papers appearing in the American Journal of Physiology, May, 1916.[1] In one of these papers (Lee, Guenther and Meleney) it is mentioned that the authors could find in the literature no comparative histological study of the muscles under discussion, namely, the diaphragm, the extensor longus digitorum, the sartorius and the soleus. From their own histological observations they were not able to point out any striking differences between these muscles.

In the present experiments these four muscles from 12 cats (young and adult) have so far been examined. The tissue was fixed in 20 per cent formalin, and frozen sections were stained with Sudan III by Herxheimer's method. This method is well adapted to the demonstration of the dual structure of muscle as seen in the so-called light and dark or cloudy fibers. The occurrence of an intermixture in varying proportions of these two types of fibers in the skeletal muscles of many animals, including probably all vertebrates, has been known for a long time (Knoll[2]). As is also well known, light fibers usually have a few small fatty droplets in their cytoplasm; dark fibers have many larger fatty droplets. Intermediate fibers also occur which are also fatty and probably belong to the dark type.

The four different muscles of the cat may be characterized briefly, as follows: Diaphragm (Fig. 1): Light and dark fibers in about equal numbers, a small number of intermediate fibers. The average

* Published in the Proceedings of the American Association of Anatomists, Anatomical Record, 1917.

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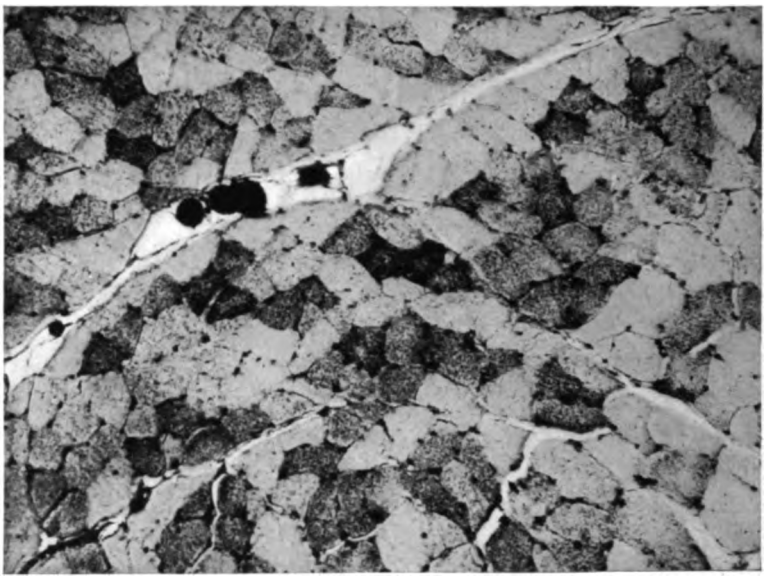

FIG. 1.—Diaphragm (×200) showing light, dark and intermediate fibers. Fat droplets in intermediate and dark fibers appear as small dark points. The fibers contain numerous very small droplets which are visible only with high magnification and do not appear in the photograph. The average diameter of the muscle fibers is less than in the other three muscles.

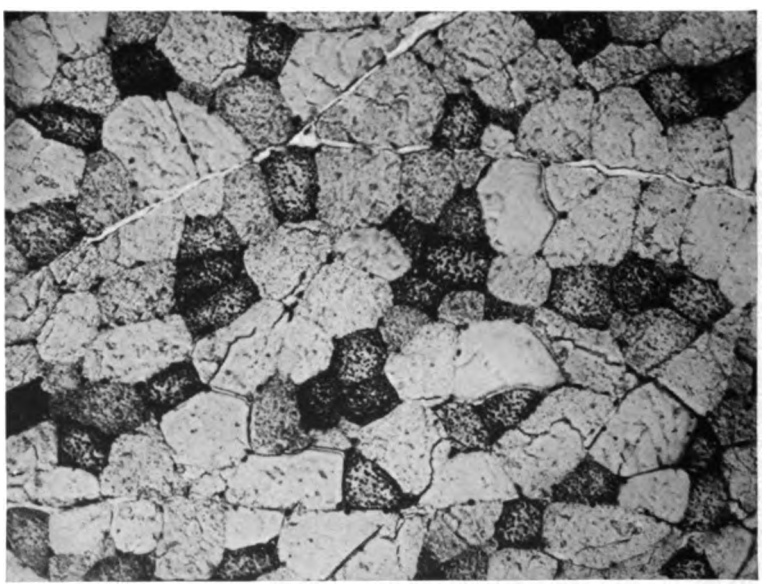

FIG. 2.—Extensor digitorum longus (×200). Light fibers are large and numerous; dark and intermediate fibers are smaller and contain fat droplets.

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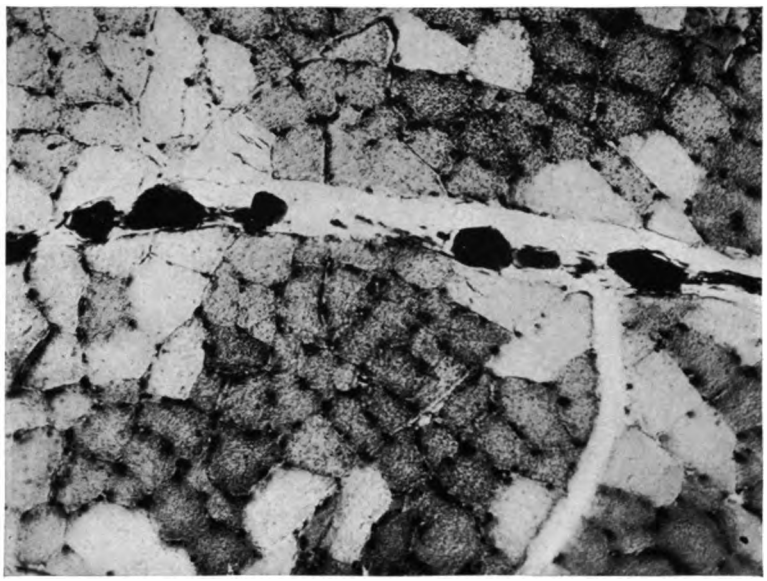

FIG. 3.—Sartorius (×200). Dark fatty fibers predominate, light fibers are larger. Several adipose tissue cells (black) are seen in the interfascicular connective tissue.

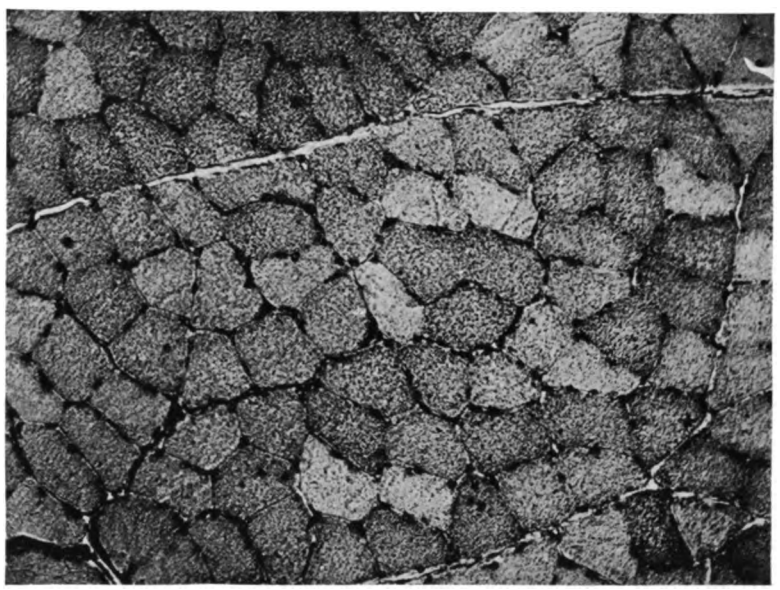

FIG. 4.—Soleus (×200). Intermediate and dark fibers predominate. There are numerous fat droplets in all the fibers. The average diameter of fibers is greater than in the other three muscles.

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diameter of the fibers is less than in the other three muscles. Extensor digitorum (Fig. 2): The light fibers form more than half the total number; the dark and intermediate are about equal in number. The average diameter of the fibers is greater than in the diaphragm and less than in the soleus. Sartorius (Fig. 3): The dark fibers predominate; the intermediate and light fibers are about equal in number. The average diameter of the fibers is greater than in the diaphragm and less than in the soleus. Soleus (Fig. 4): The intermediate fibers predominate; the dark fibers are present in considerable numbers; the light fibers are either absent or of very infrequent occurrence. The average diameter of the fibers is greater than in the other three muscles.

In all four muscles light fibers are of greater diameter than dark. When these four muscles only are considered, the microscopical picture of each is usually sufficiently characteristic to permit of its identification. From the predominance of intermediate and dark fibers, it is always possible to identify the soleus, in transverse section, from a single low power field. The predominance of light fibers serves for the easy identification of the extensor digitorum. The diaphragm and sartorius are frequently identified only after several fields have been examined; exceptionally, one of these muscles is mistaken for the other.

The extensor digitorum and sartorius are macroscopically pale muscles. The soleus is a red muscle and the diaphragm is intermediate in color. It is not true, however, that the dark fibers of the soleus are the cause of the dark or red color of that muscle. Dark fibers have their characteristic appearance only when seen by transmitted light under the microscope. By reflected light they appear light. It follows that dark fibers tend to make the muscle appear pale, and the dark red color of the soleus is not due to its dark fibers. Moreover, it is known that many pale muscles are composed largely of fibers that microscopically are dark.

The extensor digitorum, according to Lee, is characterized by great irritability—a short latent period and quick contraction and relaxation, whereas the soleus is less irritable, and after a longer latent period it contracts and relaxes slowly. As mentioned above, the histological picture shows a great predominance of light fibers in the quick muscle (extensor), and a predominance of intermediate and dark fibers, with almost total absence of light fibers in the slow muscle (soleus). The diaphragm and sartorius occupy an intermediate position both in

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these physiological properties and in the relative number of light and dark fibers. It is probable that these facts are related.

In the present experiments the histological findings in respect to the relative fat content of the four muscles agree with the chemical analyses of Lee. The extensor digitorum, chemically and microscopically, shows considerably less fat than do the other three muscles. Moreover, the quantity of fat microscopically demonstrable in each of the muscles is so great that it would appear to account for the entire quantity shown by chemical analysis. This is not in accordance with the accepted view that much of the fat in the tissues is chemically combined and not capable of microscopical demonstration.

In fasting animals, Lee has shown that the total working power of the diaphragm is reduced by 44 per cent, and the working power of the extensor by 16 per cent. It is known that fat gradually disappears from the dark fatty muscle fibers of fasting animals (Knoll,[2] Bell,[3] Bullard [4]). As we have seen, the diaphragm of the cat contains many more fatty fibers than the extensor. When the fat is removed by starvation one would expect the diaphragm to undergo a greater proportional reduction of working power.

It is scarcely necessary to mention that the microscopical differences between the four muscles under discussion are not considered exhaustively here. Interesting details respecting nuclear and myofibril characters, the occurrence and distribution of mitochondria and glycogen, blood and nerve supply and connective tissue distribution, all remain to be investigated. A study of the length of the muscle fibers by the methods recently described by Huber [5] might also prove of considerable interest.

There is good reason to believe that the striking physiological and chemical differences which Lee and his collaborators have demonstrated in these four muscles are paralleled by no less remarkable morphological differences.

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EXPLANATION OF FIGURES.

The figures are photo-micrographs of transverse sections of different muscles of an adult cat. The sections were cut on a freezing microtome and stained for fat with Herxheimer's Sudan III. All the photographs were made with Leitz Obj. 4, Oc. 1, and are reproduced full size, ×200.

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A METHOD OF CLEARING FROZEN SECTIONS.

By H. HAYS BULLARD.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

Frozen sections stained for fat with Herxheimer's alkaline-alcoholic Scharlach R are more transparent and show more detail than do sections which have not been treated with the alkaline solution. This suggested the use of alcoholic NaOH as a clearing solution. Even thick sections cleared by this method show a satisfactory sharpness of cell detail. The clearing action of the NaOH is apparently dependent upon the partial transformation of protein into the less opaque alkali-albuminate.

The best photomicrographs of frozen sections in the literature known to the writer were published by Ewald and Schaefer[1] in 1913. It is significant that these authors used Herxheimer's method, although they do not place any emphasis upon its advantages in photomicrography.*

The following is the method in detail:

1. The material is employed fresh or after fixation in formalin or formalin-saline.

2. Sections are cut on the freezing microtome as thin as practicable, and put into water or 30 per cent alcohol.

3. Transfer sections to 60 per cent alcohol for from two to three minutes.

4. Transfer sections to an alkaline alcoholic solution (formula given below) for from 5 to 15 minutes. If it is desired to stain fat, the clearing solution is omitted and in its place is substituted Herxheimer's Scharlach R or Sudan III, in a tightly closed dish for from 5 to 15 minutes (formula given below).

5. Wash sections in 60 per cent alcohol for about 20 seconds; then transfer to 30 per cent alcohol and to several changes of distilled water for from 15 to 20 minutes.

* The photographs published by the writer in a separate paper in the present number of this journal are made from frozen sections stained for fat by Herxheimer's method. Although these photographs are presented in no sense as models, it is believed that they represent an advance over those to be secured from frozen sections by other methods.

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6. Stain in hematoxylin (formula given below) for from 1 to 15 minutes. The exact time required depends upon the reaction of the tissue and must be determined by experiment. If the time is properly regulated, the nuclei stain intensely enough; cytoplasm, connective-tissue fibrils, etc., are not colored.

7. Wash in distilled water and mount in glycerine or levulose syrup (crystals). Acid alcohol and ammonia water are not used. Aqueous eosin may be used as a counter-stain, but should not be employed when the fat stain is used.

Clearing Solution.—This consists of from 55 to 70 per cent alcohol in which is dissolved 0.5 to 2 gm. of NaOH to 100 c. c. of solution. The more aqueous solutions (55 to 60 per cent alcohol) exert a greater clearing action, but with these solutions tissue sections are, in some cases, so much softened that they are easily distorted while being stained and mounted. This is particularly true when fresh unfixed material is employed. The clearing action of the 70 per cent solution is less pronounced. With this solution, however, sections are not easily distorted. The exact strength of alcohol and of NaOH which will give the desired result with any given tissue must be determined by experiment in each case. Sixty per cent alcohol with 1 gm. of NaOH to 100 c. c. of solution is usually satisfactory.

Herxheimer's Fat Stain.—The formula for this stain was published by Herxheimer[3] in 1901. It is a very concentrated solution and gives precipitates unless carefully handled. As pointed out in a previous paper,[4] Herxheimer's stain, when properly used, gives results superior to those obtained with osmic acid or simple alcoholic solutions of Scharlach R or Sudan III.

The formula is as follows:

70 per cent alcohol.....100 c. c.
NaOH ..... 2 gm.
Scharlach R or Sudan III to saturation.

When first prepared, the stain, in a loosely corked bottle, may be heated in a water bath. It should not be boiled and should stand for 24 hours before being used. One may, in some cases, secure beautifully clear sections by preparing the stain with from 55 to 60 per cent alcohol instead of 70 per cent. Keep tightly stoppered and filter immediately before using. (The method of using is given above.)

Hematoxylin Solution.—For frozen sections cleared in alcoholic NaOH, or after Herxheimer's stain, hematoxylin of the following

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formula gives more satisfactory results than other hematoxylin solutions which were tried.

Distilled water	**24 c. c.**
Glacial acetic acid	**1 c. c.**
2 per cent potassium alum (aqueous)	**50 c. c.**
1 per cent hematoxylin in absolute alcohol	**10 c. c.**
0.1 per cent chromic acid (aqueous)	**5 c. c.**
Pure glycerine	**10 c. c.**
Thymol, a small crystal.	

The solution is ready for immediate use and keeps for from six to eight months. (Keep tightly stoppered.) Filter immediately before using and use full strength. (The method of using is given above.)

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ON THE OCCURRENCE AND SIGNIFICANCE OF FAT IN THE MUSCLE FIBERS OF THE ATRIO-VENTRICULAR SYSTEM.

By H. HAYS BULLARD.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

This paper is a statement of conclusions drawn from the study of the microscopically demonstrable fat content of the muscle fibers of the atrio-ventricular system in 27 human hearts. In discussing this special feature of the pathological anatomy and physiology of the A. V. S., it is of interest to recall some of the reasons, apart from the occurrence of spontaneous and experimental heart-block, that we now have for considering this system an anatomical and physiological entity.

Mall [1] has worked out the development of the A. V. S. in the human heart. He finds that the fibers of the bundle do not grow down from the sinus, as was held by Retzer,[2] but develop from the posterior wall of the atrial canal. Histological differences between muscle fibers of the A. V. S. and cardiac muscle have been described by Purkinje,[3] Tawara,[4] De Witt [5] and others. A special relatively independent blood supply for the bundle has been described by Keith and Flack [6] and by Mönckeberg,[7] and an independent nerve supply by Wilson,[8] Morison,[9] and Engel.[10] Tawara [4] pointed out that the A. V. S. is isolated from the cardiac musculature by a connective-tissue sheath. Remarkably complete injections of the sheath have been made by Lhamon,[11] Cohn [12] and others. Injections of the sheath in human and dog hearts are less successful than in the sheep, ox or pig. Aschoff [13] and Mönckeberg [14] observed that the bundle is unaffected in both atrophy and hypertrophy of the heart. Marchand [15] found a higher glycogen content in Purkinje fibers than in cardiac fibers. This observation was confirmed and extended by Aschoff and Nagayo.[16]

The occurrence and significance of fat in cardiac muscle fibers is to be here considered only for the purpose of comparing it with the fat content of the A. V. fibers. It may be well, however, to mention that a number of investigators have observed fat in the apparently normal cardiac muscle of various animals, including, in certain cases, man

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(Ostertag,[27] Ricker and Ellenbeck,[28] Fibiger,[29] Arnold,[30] Keinath,[31] Babes,[32] Hofbauer,[33] Bell,[34] Wegelin [35]). Knoll [36] found that during starvation fatty droplets disappear from the skeletal and cardiac muscle of pigeons. In the skeletal and cardiac muscle of normal rats, Bell [34] demonstrated an increase in the fat content of the fibers when fatty foods were given, and a decrease or total disappearance when all food was withheld. After a study of 200 hearts from rats, cats, dogs, oxen, sheep, pigs and other animals, the writer [37] came to the conclusion that a variable amount of microscopically demonstrable fat is normally present in cardiac muscle and in fibers of the A. V. S.

Technique.—The material was obtained as soon after death as possible, and only from bodies in which little post-mortem change had occurred. In animals it is found, in certain cases, that fat in tissue cells readily undergoes obscure post-mortem changes that make its microscopical demonstration difficult or impossible. Frozen sections were made from fresh material, and also from that which had been fixed for a few hours in 20 per cent neutral formalin. Frequently with the tissue of the fetus and young individuals and less frequently with those of adults, it is observed that little or no fat can be demonstrated in sections after formalin fixation, although a considerable amount may have been stained in the fresh tissue. It is, therefore, necessary to use sections or teased preparations of the fresh material for controls. Sections of formalin-fixed material, however, are usually more satisfactory for study. The sections were stained with Sudan III and Scharlach R by Herxheimer's method. The method has marked advantages over others in common use, and is given in detail in the paper on the clearing of frozen sections published in the present number of this report.

Chemical Nature of Fat.—The term *fat,* as used in this paper, includes all droplets which stain intensely with Herxheimer's Scharlach R and Sudan III. These droplets are completely dissolved out of tissue sections by absolute alcohol, ether and other fat solvents. Tests made on a considerable number of specimens show that the droplets are not doubly refractive, are not easily rendered insoluble by potassium bichromate and do not stain with basic aniline dyes. This combination of properties makes it seem probable that the droplets are predominately neutral fat and not a cholesterin compound or phospho-lipin. Fatty pigment or lipochrome is colored by Scharlach R and by Sudan, but on the basis of morphology and cytological

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relations is easily distinguishable from the fat droplets. In the findings given in the table, fatty pigment is not included.

No.	Sex.	Age.	Anatomical diagnosis.	Amount of fat in cardiac fibers of interventricular septum.	Amount of fat in left branch of His bundle.
1	M..	5 mos. fetus..	Prematurity.....	Moderate..	Small.
2	F..	5 mos. fetus..	Prematurity.....	No fat....	No fat.
3	M..	7 mos. fetus..	Prematurity.....	Moderate..	Moderate.
4	F..	7 mos. fetus..	Prematurity.....	Moderate..	Small.
5	F..	8 mos. fetus..	Prematurity.....	Moderate..	Moderate.
6	M..	8 mos. fetus..	Prematurity.....	Small.....	Moderate.
7	M..	3 weeks.....	Pulmonary atelectasis, broncho-pneumonia, fatty liver.	Small.....	Moderate.
8	F..	4 months...	Purulent meningitis, broncho-pneumonia.	Moderate..	Large.
9	M..	7 months...	Erysipelas, broncho-pneumonia, syphilis.	Small.....	Small.
10	F..	8 months...	Broncho-pneumonia.....	Moderate..	Moderate.
11	M..	1 year.....	Necrotizing laryngitis and tracheitis, broncho-pneumonia.	Small.....	Moderate.
12	M..	4 months...	Syphilis, broncho-pneumonia	Small.....	Small.
13	F..	3 years.....	Empyema, fibrino-purulent peritonitis and pericarditis, syphilis.	Moderate..	Moderate.
14	F..	15 years....	Multiple conglomerate abscesses of kidney.	Small.....	Large.
15	F..	34 years....	Fibrinous peritonitis, broncho-pneumonia.	Moderate..	Moderate.
16	M..	37 years....	General miliary tuberculosis.....	Small.....	Moderate.
17	F..	40 years....	Acute endometritis and salpingitis.	Moderate..	Large.
18	M..	40 years....	Purulent meningitis, cerebral abscess.	Small.....	Large.
19	M..	42 years....	Chronic diffuse nephritis.....	Small.....	Large.
20	M..	44 years....	Extensive superficial burns, broncho-pneumonia.	Very small.	Moderate
21	F..	47 years....	Pernicious anemia.....	Large.....	Large.
22	M..	49 years....	Glioma of brain, broncho-pneumonia.	Small.....	Large.
23	F..	50 years....	Exophthalmic goitre, excision of right lateral lobe of thyroid.	Large.....	Very large.
24	M..	50 years....	Chronic ulcerative pulmonary tuberculosis, broncho-pneumonia.	Very small.	Moderate.
25	M..	59 years....	Syphilis of aorta and aortic valve, fibrinous pericarditis, broncho-pneumonia.	Moderate..	Large.
26	M..	62 years....	Lobar pneumonia, acute vegetative mitral endocarditis.	Very small.	No fat.
27	M..	71 years....	Periurethral abscess, thrombosis of femoral vein.	Very small.	Small.

Occurrence of Fat in Cardiac Fibers.—In the case of pernicious anemia, No. 21 in the table, the heart muscle presented typical patho-

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logical fatty change both macroscopically and microscopically. The fatty mottling of the myocardium was very pronounced. In other cases listed in the table, the fat was not evident macroscopically, although in most cases it was demonstrated in considerable amounts microscopically. Eyselein [28] reports somewhat similar observations. He demonstrated fat microscopically in the muscle fibers of 25 per cent of 385 human hearts, although he was able to observe typical fatty mottling in a comparatively few cases. In most of the cases reported in this paper, fat droplets are present in nearly every fiber. Some fibers are much more fatty than others. The individual droplets occur in longitudinal and transverse rows between the myofibrillæ. The muscle fibers show no degenerative changes. From an examination of these and other cases, the writer is of the opinion that man is no exception to the rule that microscopically demonstrable fat occurs normally in cardiac muscle.

Occurrence and Distribution of Fat in A. V. Muscle Fibers.—Reference to the table will give some idea of the general occurrence of fat in fibers of the bundle in the cases examined. The findings given in the table are based on an examination of sections cutting the left branch a short distance from its origin. In each case several sections from this situation were examined, and in many cases sections were also cut from the right branch as it crosses in the moderator band, from the bases of the papillary muscles, and from the node and main stem of the bundle. In nearly all cases numerous very small fat droplets were scattered irregularly in the muscle fibers of the node. The total quantity of fat in the fibers of the node was, however, quite small in every case. The stem of the bundle shows more fat than does the node, but less than the two main branches or the end branchings. Of the 27 cases listed in the table, at least a small amount of fat was present in fibers of the left branch of the bundle in 25 cases. The amount of fat in the fibers of the right limb and in the end branches was similar to that observed in the left branch.

The distribution of the fat was rather irregular. In several cases all the fibers contained numerous fine droplets averaging 1μ in diameter. In a second group of cases the droplets averaged from 2 to 3μ in diameter, and occurred usually in groups or clusters in certain fibers, others being apparently fat-free. In the group of cases showing a large amount of fat, nearly all the fibers contained numerous large and small droplets. In all cases the droplets were in the cytoplasm, not in the

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fibrillæ. No constant arrangement of fat with respect to the nuclei was observed.

Relation of Fat in A. V. Fibers to That in Cardiac Fibers.—Mönckeberg [14] observed the occurrence of fat in the A. V. fibers unaccompanied by fatty cardiac fibers. His observations have been confirmed by some and denied by others. In three cases listed in the table, the A. V. fibers show less fat than the cardiac fibers, in nine the quantity is approximately the same in the two, in 15 the A. V. fibers have more than the cardiac. In a majority of cases the quantity of fat in the A. V. fibers is greater than in the cardiac fibers. This is in agreement with the findings of Engel,[19] and contrary to those of Sternberg,[20] Löw [20] and Monrad-Krohn.[21] Although the amount of fat in the two sets of fibers does not run parallel, the divergence is not so great as one would expect if there were absolutely no common factors concerned in the production of fat in the two situations. In the human heart a large or small amount of fat in the cardiac fibers usually indicates a somewhat similar and but slightly larger amount in the A. V. fibers. A sufficient number of cases, however, show a wide divergence in the amount of fat in the two situations (Cases 14, 18, 19, 22). In these cases the amount of fat in the cardiac fibers is so small that it would be easily overlooked if osmic acid or simple alcoholic solutions of Sudan III or Scharlach R had been used as stains. If we disregard this small amount of fat in the cardiac fibers we may consider these cases as a confirmation of Mönckeberg's observations on the occurrence of isolated fatty A. V. fibers.

A comparison of the fat content of the A. V. and cardiac fibers in animals is of interest. In the 30 hearts of cats previously described by the writer, eight had more fat in the Purkinje fibers, six had more in the cardiac fibers, and in 16 animals the amount in the two sets of fibers was approximately equal. In six hearts of dogs the A. V. contained slightly less fat than the cardiac fibers. In the pig, sheep and ox (22 animals) the A. V. fibers contained only a small amount of fat, and this was so even when the cardiac fibers were very fatty. In sections stained with Herxheimer's Scharlach or Sudan, the almost fat-free A. V. fibers were easily followed for long distances among the fatty cardiac fibers, especially in the papillary muscles. This normal condition in the hog, sheep and ox is in striking contrast with conditions observed in the human heart where it is frequently possible to

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trace the A. V. system because of its predominately fatty fibers. The heart of the cat in this respect resembles the human.

Relation of Age to Fat Content of A. V. Fibers.—In the cases here reported fat occurs in the A. V. fibers in the fetus, in children and in adults both young and old. Apparently there is little or no relation between fat in the A. V. fibers and the age of the person. The same is true in animals where fat occurs in the fetus as well as in adults. Engel [30] and Aschoff [31] found no fat in the A. V. fibers of the human heart in subjects under 40 years of age. The amount of fat in Purkinje fibers was thought to increase with age. It is probable that the results here reported differ from those of Engel and Aschoff primarily because of factors which have been mentioned under the heading of *Technique.*

Physiological Significance of Fat in A. V. Fibers.—Fat in the A. V. fibers is by different authors associated with cardiac irregularities and sudden death (Mönckeberg [34]), cardiac irregularities in toxic conditions, especially in diphtheria (Amenomiya,[32] Tanaka [33]), senile or pre-senile changes (Aschoff, Engel), and it has been reported as the principal lesion in a case of heart-block (Butler [34]). In the small number of cases here reported, it has been impossible to determine any relation between the occurrence of the fat and definite clinical manifestations or associated pathological conditions. Clearly the occurrence of fat in the A. V. fibers is not to be regarded as a senile change, neither is it a sufficient anatomical finding in cases of heart-block.

The regular occurrence of fatty A. V. fibers in the hearts of animals and apparently in the human heart naturally suggests the idea that its presence is concerned with normal and not pathological metabolism. This is rendered the more probable by the absence in these cases of associated pathological changes in the A. V. fibers. We now know that fat can be microscopically demonstrated in the normal cells of many organs, and under strictly physiological conditions the amount in the cells of a given tissue may vary between wide limits. Pathologically, the normal picture is to a greater or less extent changed as the result of altered cell metabolism following certain toxic conditions and circulatory disturbances. It is probable that the same is true of fat as it occurs in the A. V. fibers. In order to define accurately the normal picture of the fat content of these fibers, together with some of the pathological variations, it will be necessary to examine a greater number of cases than are here reported.

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Summary and Conclusions.

In this investigation the muscle fibers of the atrio-ventricular system of 27 human hearts were examined microscopically for fat. In 25 cases fat droplets were demonstrated in the sarcoplasm of the fibers. The fibers of the A. V. node contained little fat. A considerable amount occurred in fibers of the right and left branches and in the end branches. In most cases more fat was present in the A. V. fibers than in the cardiac fibers. The occurrence of fat in the A. V. fibers of normal animals is also discussed.

Fat in the muscle fibers of the A. V. S. is by different authors associated with senile changes, cardiac irregularities, sudden death, and heart-block. In the cases here reported no relation is observed between the age or clinical conditions and the occurrence of fat in the fibers.

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STUDIES ON THE METABOLISM OF CELLS IN VITRO.*

I. The Toxicity of α-Amino-Acids for Embryonic Chicken Cells.

By MONTROSE T. BURROWS, M.D., and CLARENCE A. NEYMANN, M.D.

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A synthetic medium suitable for the growth of tissue cells outside of the animal organism has not been discovered up to the present time. Since the preparation of such a medium would lead directly to a better understanding of cellular metabolism, this problem has stood forth as one of the most important of those presented by the tissue-culture method.

From earlier observations evidence had already been obtained which showed that the ingredients essential for the building of new cells and the liberation of energy in the cultures come directly from the tissue fragments. The growth observed is a manifestation of a simple transfer of materials from the more central portions of the fragment to the cells at the periphery, or, in other words, the preying of one cell in a more suitable environment upon its neighboring cells in an unsuitable one. This is true in cultures where simple isotonic salt solutions have been used as the media. That it is also true in the case of the plasma culture can be readily shown by repeatedly changing the medium or transplanting the cells to drops of fresh medium. All activity ceases after a few transplants, or when the cells within the fragment have become exhausted.

One of us,† in a recent study, has shown that tissue cells are not highly organized elements. Their various manifestations of life are the result of reactions between themselves and a specifically organized environment. The form of the manifested change is determined by the peculiar organization and composition of the environment. Growth

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† Read before Section VIII, Subsection E, Second Pan-American Scientific Congress and the American Cancer Society, Washington, January 6, 1916.

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associated with mitotic cell division is seen only in cells which have become passively placed at the interspace between certain insoluble substances and the medium. These substances are liberated from the cells when they are removed from their normal habitat to an oxygen-containing plasma or salt solution. The substances are almost transparent, their refraction is not very different from that of the original medium, and they accumulate at the surface of the medium to form a membrane. They are liberated in large amounts from a tissue-fragment rich in cells.

A cell brought in contact with the surface of this transparent substance adheres to it and flattens over its surface. Such a cell grows and divides by mitosis when oxygen is present and the waste products remain below a certain concentration.

A single isolated cell when placed in a drop of fresh plasma does not grow and divide. It may show movement. Connective-tissue cells often assume spindle and irregular stellate shapes. These simple activities lead, however, apparently to the exhaustion of these cells. They come to rest after a short period and show evidences of deterioration through vacuolization and failure to stain sharply.

All cells that grow in these cultures grow at the expense of their neighbors. In the culture the cells at the border of the fragment grow; they have come in contact with a layer of the transparent substances mentioned above, which was liberated by the large number of cells deteriorating in the center of the fragment. These cells within the fragment about which the border cells are growing actively soon become reduced to mere shadows. This deterioration goes on to such an extent that they no longer stain.

With the increase in the concentration of the waste products, the activity of the cells in the outer medium not only becomes less and less, but there is also a decrease in the liberation of substances from the fragment. Eventually the whole system comes to a state of complete inactivity or equilibrium. Such a system remains without further change often for a period of time, sometimes as long as six months, at incubator temperature and in the presence of an ample supply of oxygen. If the cells and the fragment at any time during this period are removed to a fresh medium, normal activity is again observed, provided the fragments and the cells have not been transplanted frequently at a previous time, or become exhausted of this substance, or of substances which lead to its formation.

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If cells are placed in a medium where the mechanical conditions are such that these substances cannot diffuse out from the fragment over a surface, or the cells are prevented from coming in contact with this surface, growth followed by mitotic division does not take place, but other forms of change result. By merely changing the mechanical organization of the culture or changing the differential surface tension of the cell, it has been found possible to change its form, structure and the manifested activity associated with it. Heart muscle cells, when placed in a medium where they may be passively carried against the flat surface of these substances, lose their myofibrillar structure and grow and divide by mitosis. They resemble in every way growing sarcoma cells. The same cells may again be caused to grow to form a syncytium, their nuclei dividing by a mitosis. Again, they may be caused to round off and resemble large mononuclears, or to differentiate into myofibrils and *vice versa*. The contracting heart muscle cell is a cell which has become stretched through a serum cavity between the surface formed by the substances diffusing from the fragment and an elastic band of fibrin. One end is adherent to the surface and the other to the end of the band of fibrin. The cell is elongated and spindle in shape. Its elongated shape is maintained by the stress of the fibrin. The surface of the cell, which is unattached to the fibrin or the surface of the substances coming from the fragment, is sharply defined. It has a high surface tension. The points of active change in such a cell are evidently the points of contact.

The cells of higher animals are, therefore, strikingly different from many unicellular organisms, such as the paramecium etc., which contain within themselves all the necessary organization for their growth. Growth and the various manifestations of life of the animal cell are differential surface tension phenomena which are under the control of the environment. Their manifestations of life are manifestations of "tissue rather than cellular reaction." †

The growth of the cells in the culture depends upon the presence of certain specific substances which are liberated by their neighbors and a specifically organized environment. The growth itself is evidently a highly specific reaction. It is a reaction which one might readily assume would continue as long as these specific substances are liberated from the fragment, the proper mechanical organization is maintained about the cells, ample supply of oxygen is present, and the waste products of the reaction are removed.

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The questions that confronted us primarily in a further study of these cultures are: What is the nature of these substances? How are they formed in the body under normal conditions? Can any part of the body live an independent existence when isolated from the other parts? Is the organization of the culture such that it will be able to form these substances from simple food bases? The unicellular organism is capable of breaking down complex substances and building its various component parts from the products liberated. Are these systems which have been isolated, tissue cultures, also capable of an independent existence? Is the failure to demonstrate any actual increase of protoplasm in the plasma culture indicative that these organizations are not able to live an independent existence, to build these substances from the food bases, or is it indicative merely of the lack of the proper food bases in the plasma which has been used as a medium?

The fact that plasma contains carbohydrates, proteins, and fats made it seem plausible to assume that these systems are unable to utilize them directly as food substances. That in the ordinary plasma cultures these food bases are insufficient for the building of new cells can be shown definitely not only by the failure of the cells to continue to grow after several transplants, but further by actual measurements. The sum of the masses of new cells formed in each transplant is always less than the original mass. One could readily consider in a well-regulated series that it represents the original mass minus the energy of transfer.

Experimental.

In the present series of experiments we tried to determine whether the addition of any substance to the plasma would prolong the growth of the cells. The addition of certain carbohydrates and fats did not affect the growth to any degree. During the course of further experiments we had the opportunity to try certain hydrolytic products of the protein of egg-yolk. Since the results of these experiments have a certain interest in themselves, we decided to report them separately at this time.

Method.

The tissues used for these experiments were heart muscle and pieces of the body wall of chick embryos and fetal chickens. The control medium for the experiments consisted of one part of fresh plasma, containing a moderate amount of fat, and one part of a 0.9 per cent

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sodium chloride solution. In the experiments the same proportions were used: one part of the isotonic solution of the substance to be tested was added to one part of the same plasma.

Fragments of heart muscle 1 mm. in diameter are placed in a layer of medium spread over the surface of a cover-glass. This layer has a thickness of 0.5 mm. A hollow ground slide is inverted over the drop, and the edge of the cover sealed to the slide with vaseline and paraffin. The cultures are placed in an incubator kept at a constant temperature of 39.4° C. They are examined under a microscope that is kept in a chamber heated to the same temperature as that of the incubator.

After three days' incubation, the growth of each is recorded and the fragment with the cells about it from each of the cultures is carefully transferred to a new drop of the medium, in which it has been previously grown. At the end of another three days the growth is again recorded and the fragments and cells are again transplanted, and so on until no more activity is seen.

The growth in these cultures takes place as a rule along a single plane. A rough estimate of activity can be made by measuring the area covered by new cells about a fragment. There are always, however, a number of cultures in which the cells grow in several planes. On this account we have decided that a more accurate estimate can be given by the use of a relative term +, rather than by the direct numerical measurements. In the tables we have used this method of recording activity.

Plasma has been used in these experiments not only because it was of interest to test this medium more carefully, but also because when it is used it is possible to obtain a constant and readily predicted cellular activity in the control cultures. This has not been found to be true for any of the simple liquid media. The proper mechanical conditions in the latter cultures are difficult of manipulation.

In the first series of experiments, we prepared peptones from the yolks of eggs; that is, they were prepared from the specific food proteins of the embryonic chicken cells. These peptones were obtained by the use of the general method described by Abderhalden * and slightly modified by us as follows: 240 gm. of coagulated egg-yolk are dried and pulverized, and treated with 1000 gm. of 70 per cent (by weight) of pure sulphuric acid. The coagulated yolk does not dissolve as

* Abderhalden, E., Defensive Ferments of the Animal Organism, New York, 1914, 204.

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readily as one might wish, so the mixture is shaken vigorously for an hour. A thick scum forms on the top, the rest of the material going into solution. This scum is removed. It proves to be fat. The brownish purple solution is next allowed to stand at room temperature for three days. It is frequently shaken during this time and then transferred into a 20-liter mixing jar, the latter being packed in a freezing mixture where it is cooled thoroughly. Ten liters of water are then added very slowly, while stirring, keeping the temperature below 20° C. After this, enough barium hydroxide in crystalline form is added to give the solution a neutral reaction towards litmus. This process requires great care. It is best to calculate the exact quantity of barium hydroxide needed, to add nearly this quantity, and then proceed gradually. The solution must be stirred constantly in order to keep the temperature below 20° C. at all times. The voluminous precipitate of barium sulphate is best separated from the digested solution by means of a centrifuge. This solution is next treated alternately with 0.1 N barium hydroxide and 0.1 N sulphuric acid until the addition of an excess of either to a filtered or centrifuged sample does not give a further precipitate of barium sulphate. Of course, an addition of barium hydroxide to a peptone solution will sometimes give a precipitate of barium peptonates, but these are soluble in dilute nitric acid, while barium hydroxide is not. Thus an absolutely neutral solution is prepared. This solution of over 10 liters in quantity is next concentrated under reduced pressure until about 100 c. c. of a syrupy, light yellow liquid results. This is treated with about 2 liters of hot methyl alcohol and filtered into 10 liters of chilled ethyl alcohol. A white precipitate results, and is quickly filtered off by the aid of a suction pump and dried in a desiccator. The color of the resultant powder is light yellow.

These peptones gave all the true peptone reactions. They were absolutely soluble in a saturated solution of ammonium sulphate and remained unchanged as regards color on boiling with a solution of sodium hydroxide, to which a drop of lead acetate solution had been added. They were dialyzable through a dialysis tube impervious to albumin, and the dialysate gave a typical blue ninhydrin reaction. Finally, they gave a reddish biuret reaction, and their microscopic appearance was similar to that of commercial silk peptone.

A large amount of this peptone, namely, 2.5 per cent, can be dissolved in 0.85 per cent sodium chloride solution, without making the

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solution hypertonic and thereby killing the cells. This solution is mixed half and half with plasma. The growth, as is shown in Table I,

TABLE I.

Tissue: Fragments of the heart muscle of a 12 day old chicken embryo.
Medium: Isotonic solutions of peptone, 2.5 per cent, in sodium chloride solution, 0.85 per cent, 1 part.
Plasma, 1 part.
Control Medium: Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 1 part.

Solution used.	Culture No.	Growth of transplants.						
		1st.	2d.	3d.	4th.	5th.	6th.	7th.
Peptone.	1	++++	++++	++	+	0	0	0
	2	+++	++++	+++	++	Few cells.	0	0
	3	+++	+++++	+++	+++	+	Few cells.	0
	4	++++	++++	++++	+++	++	Few cells.	0
	5	++++	+++++++	++++++	++++++	0	0	0
Control.	6	+++	+++++	—*	—	—	—	—
	7	+++++	++++++	++++	++	0	0	0
	8	+++	++++	++	++++++	++	Few cells.	0
	9	+++++	+++++++	++++++	++++	0	0	0
	10	+++	++++	++	++	Few cells.	0	0

*In the tables the dashes indicate that the culture was lost through breaking of the glass slide, infection, or other causes.

Cultures 1, 2, 3, 4, and 5, continued regularly up to the sixth transplant. After this the various fragments became exhausted. The control cultures, 6, 7, 8, 9, and 10, behaved in exactly the same manner. From this we conclude that peptones do not in any way enter into this growth reaction. They did not prolong it, and no change of any kind was noted from their addition.

We next turned our attention to the study of *a*-amino-acids. The complete hydrolysis of egg-yolk promised a yield of *a*-amino-acids in the same proportions as they actually occur in the protein molecule, the only *a*-amino-acid which does not give a yield on acid hydrolysis being tryptophane. This seemed to be the easiest and most direct way of procedure. Consequently a digestion mixture was prepared by

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dissolving dried egg-yolk, from which the fats had been extracted with ether by means of a Soxhlet apparatus, in a 70 per cent (by weight) solution of sulphuric acid. After the protein had gone into solution, enough water was added to make this a 25 per cent solution of sulphuric acid. The entire mixture was then heated in a flask with a reflux condenser until a biuret reaction was no longer obtainable. This acid solution was next neutralized with barium hydroxide in exactly the same manner as stated above for the preparation of peptones. After this the solution was concentrated under reduced pressure at 40° C. until evaporation to dryness gave a 3 per cent residue, which we believe consists for the most part of α-amino-acids. Plasma was diluted with this mixture. To our surprise all the cells were dead in 48 hours, whereas the control cultures in plasma alone grew and kept on growing as usual when they were transplanted. We did not consider this peculiar result due to the possible toxicity of the α-amino-acids as such, but thought that traces of sulphuric acid or barium hydroxide caused the death of the cells. In order to make sure that this was the case, a part of the digestion mixture was further concentrated to one-fifth of its volume, divided in two portions, and each portion tested with an excess of 0.1 N sulphuric acid and 0.1 N barium hydroxide respectively. No precipitation occurred.

Discarding the idea that a trace of sulphuric acid or barium hydroxide could be the cause for failure, we considered hypertonicity as a possibility. A simple way of testing whether a solution is isotonic or not towards chicken cells is by the use of chicken erythrocytes. The red blood corpuscles are nucleated and consequently have a bulge in the middle of the disc. This bulge is especially conspicuous when the corpuscle is seen on end. If a solution is hypotonic, the surrounding disc will swell and this bulge will become less marked. If, on the other hand, solution is hypertonic, one sees characteristic shrivelling around the edge of the disc. It is, of course, understood that extremely hypotonic or hypertonic solutions will cause a dissolution of the corpuscles, a dissemination of the hemoglobin, and give a characteristic laked appearance.

Making up various dilutions of the digestion mixture, we transferred 1 c. c. of the dilutions to suitable test-tubes and added 0.25 c. c. of a 5 per cent suspension of washed chicken erythrocytes in 0.9 per cent sodium chloride solution. We then incubated it for four hours and compared it with the form of our control diluted with 0.9 per cent

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sodium chloride solution and treated in exactly the same manner. Using the dilution which showed neither shriveling nor bulging, we prepared an isotonic digestion mixture.

Renewed experiments with the digestion mixture gave practically the same results as before. A repetition of the experiment with a new digestion again resulted in the death of the cultures. A portion of the last digestion mixture was treated with hydrochloric acid gas to the point of saturation and allowed to stand in the ice-box for several days. We obtained a voluminous precipitate of glutamic acid hydrochloride, showing its typical crystalline form. This gave the final proof that α-amino-acids were present. Even now we did not attribute our results to a toxic influence of the acids in themselves, but rather to the influence of the brown coloring matter in the solution, said to consist of caramelized carbohydrates, humin substances, etc. We therefore tried pure α-amino-acids.

We used 10 of the acids in our first experiment; namely, glycocoll, alanine, cystine, valine, leucine, phenylalanine, tyrosine, tryptophane, oxyproline, and asparagine.* Some of the substances were synthetic (Merck and Kahlbaum preparations), while others were obtained by the hydrolysis of proteins.†

To be sure of the substances which we used, the total nitrogen of each of the α-amino-acids was determined, their melting points were ascertained, and their crystalline forms observed. All these tests proved that we were dealing with chemical substances of the right molecular constitution containing no demonstrable impurities.

Hot saturated solutions of these acids were prepared. The solutions were cooled, and each solution was tested with chicken erythrocytes for isotonicity by the methods described above. The more insoluble sub-

* We used asparagine in spite of the fact that it has not been found as a constituent of hydrolyzed animal proteins. The effect as shown in the tables is exactly the same as in the case of the other α-amino-acids. Fig. 2 is a fair representative of the appearance of any one of the cultures in which α-amino-acids had been added to the medium. This culture was selected for photographing because it was prepared practically at the same time as the controls. The tissue that was used was most similar and had suffered practically the same exposure as that used for the controls.

† We wish to thank Dr. P. A. Levene, of The Rockefeller Institute for Medical Research, Dr. D. W. Wilson, of the Physiological Chemical Laboratory of Johns Hopkins University, and Dr. R. F. Ruttan, of McGill University, for supplying us with some of the acids more difficult to manufacture.

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stances, such as cystine, were primarily dissolved in isotonic salt solution, as we could hope to obtain isotonicity in no other way. All these

TABLE II.

Tissue: Fragments of the heart muscle of a 12 day old chicken embryo.
Medium: Isotonic solution of the α-amino-acid, 1 part.
Plasma, 1 part.
Control Medium: Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 1 part.

Solutions used.	Culture No.	Growth of transplants.	
		1st.	2d.
Glycocoll, 35 per cent solution,* 1 part, and water, 19 parts.	1	+++	Few cells.
	2	+++	" "
	3	+++	" "
	4	+++	0
	5	+++	—
Alanine, 11 per cent solution, 1 part, and water, 13 parts.	6	++	+
	7	+++	Few cells.
	8	+++	+
	9	+++	0
	10	+++	Few cells.
Valine, 8 per cent, 1 part, and water, 4 parts.	11	+++	Few cells.
	12	++	0
	13	+++	Few cells.
	14	+++	0
	15	++	—
Leucine, 1.66 per cent, 1 part, and water, 2 parts.	16	++++++	0
	17	++++	0
	18	+++	0
	19	++++	0
	20	+++++	0
Cystine, 0.1 per cent solution, not diluted.	21	++	0
	22	+++	Few cells.
	23	++	+
	24	+++	+
	25	+++	0
Control.	26	+++	—
	27	++++++	++++
	28	++++++	—
	29	+++++	+++++
	30	++++	++++

*All percentages given are approximate.

solutions were diluted half and half with plasma and used as culture media.

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Tables II, III, and IV give a survey of the experiments. In every case the addition of a solution of α-amino-acids to the plasma results in the ultimate death of the growing cells, while the controls keep on with their regular development. The discrepancy between the

TABLE III.

Tissue: Fragments of the heart muscle of an 11 day old chicken embryo.
Medium: Isotonic solution of the α-amino-acid, 1 part.
Plasma, 1 part.
Control: Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 1 part.

Solutions used.	Culture No.	Growth of transplants.			
		1st.	2d.	3d.	4th.
Valine, saturated solution, cold, 1 part, and water, 3 parts.	1	+	Few cells.	0	
	2	+	0	0	
	3	+	0	0	
	4	Few cells.	0	0	
Glycocoll (Merck), saturated solution, cold, 1 part, and water, 24 parts.	5	++	++	0	
	6	+++	+++	0	
	7	++	+++	0	
	8	+	+++*	0	
Asparagine, saturated solution, cold, 1 part, and water, 3 parts.	9	++	+*	0	
	10	+	+	0	
	11	+	+	0	
	12	+++	++	0	
Cystine, saturated solution, cold, 3 parts, and water, 2 parts.	13	++++++	+++	Few cells.	
	14	++++	++++	" "	+ Cells rounded off.*
	15	++++	++++	—	
	16	++++	—	—	
Controls.....	33	+++++	++++++	+	+
	34	++	+++++	+	+
	35	++	++++++	+	+
	36	+++++++	++++++++++	+	+

* All the pieces are contracting actively.

time required to kill the cultures described in Tables II and III, on the one hand, and in Table IV, on the other, the cultures of the latter series dying more quickly, is explained by the age of the embryo used. The cells of the younger embryo grow much faster and are less resistant to toxic influences than are those of an older embryo, as is known from numerous reported experiments.

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TABLE IV.

Tissue: Fragments of the body wall of a 5 day old chicken embryo.
Medium: Isotonic solution of the α-amino-acid, 1 part.
Plasma, 1 part.
Control Medium: Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 1 part.

Solutions used.	Culture No.	Growth after 48 hours.	Growth after 72 hours.
Glycocoll, 35 per cent solution, 1 part, and water, 19 parts.	1	+	The cells have all rounded off and show distortion.
	2	Few cells.	
	3	" "	
Alanine, 11 per cent solution, 1 part, and water, 13 parts.	4	+	The cells have all rounded off and show distortion.
	5	Few cells.	
	6	" "	
Cystine, 0.1 per cent solution, not diluted.	7	+	The cells have all rounded off and show distortion.
	8	+	
	9	+	
Valine, 8 per cent, 1 part, and water, 4 parts.	10	+	+++ The cells have all rounded off.
	11	++	+++
	12	++	+++
Leucine, 1.66 per cent, 1 part, and water, 2 parts.	13	++	++ The cells have all rounded off.
	14	++	++
	15	+++	+++
Phenylalanine, 2 per cent, slightly hypotonic, not diluted.	16	++	The cells have all rounded off and show distortion.
	17	—	
	18	+	
Tyrosine, 0.285 per cent in 0.85 per cent sodium chloride, 2 parts, and water, 1 part.	19	+	+ The cells have all rounded off and show distortion.
	20	++	+++
	21	++	++
Tryptophane, 1.66 per cent in 0.85 per cent sodium chloride, 1 part, and water, 2 parts.	22	++	The cells have all rounded off and show distortion.
	23	+++	
	24	++	
Oxyproline, 10 per cent, 1 part, and water, 2 parts.	25	+	The cells have all rounded off and show distortion.
	26	++	
	27	++	
Asparagine, 15 per cent, 1 part, and water, 1 part.	28	Few cells.	The cells have all rounded off and show distortion.
	29	" "	
	30	" "	
Control	31	+++	++++++
	32	+++	++++
	33	+++	+++++

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In Table V, we tried more dilute solutions and, as this table indicates, the cells tend to resist this medium for a longer time. However, none of these cultures grew as long as the controls, which shows that

TABLE V.

Tissue: Fragments of the heart muscle of an 11 day old chicken embryo.
Medium: Isotonic solution of the α-amino-acid, 1 part.
Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 2 parts.
Control: Sodium chloride solution, 0.9 per cent, 1 part.
Plasma, 1 part.

Solutions used.	Culture No.	Growth of transplants. 1st.	2d.	3d.	4th.
Valine, saturated solution, cold, 1 part, and water, 3 parts.	17	++++	—	—	—
	18	++++	+ Few cells.	0	0
	19	++	—	—	—
	20	+++	++++	+++*	+++* The cells have all rounded off.
Glycocoll (Merck), saturated solution, cold, 1 part, and water, 24 parts.	21	++++	+++++*	+++*	++++* The cells have all rounded off.
	22	+++++	+++++	+++*	0
	23	++++	++++	—	—
	24	—	—	—	—
Asparagine, saturated solution, cold, 1 part, and water, 3 parts.	25	++++	+++++*	—	—
	26	++++	+++++*	++++*	++++*
	27	—	—	—	—
	28	—	—	—	—
Cystine, saturated solution, cold, 3 parts, and water, 2 parts.	29	+++*	++++++*	+*	0
	30	+++++*	++++++	+++*	0
	31	++++*	++++++*	++++*	0
	32	++++++*	++++++*	+*	0
Controls.....	33	+++++	++++++	+++	+++++
	34	++	++++++	++++	+++++
	35	++	++++++	++++	++++
	36	++++++	++++++++	++++++	+++

* All the pieces are contracting actively.

even in very low dilutions the α-amino-acids are toxic. It is of interest in this series to note evidences of stimulation. This stimulation, as the table indicates, is not a stimulation of growth, but a stimulation of

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the contraction of the heart muscle fragments. All the fragments contracted actively with the exception of the controls. This contraction continued to the complete exhaustion of the fragments.

Discussion and Summary.

Summing up these results, we found that all the 10 α-amino-acids used inhibited the growth of the cells and finally killed the cultures.

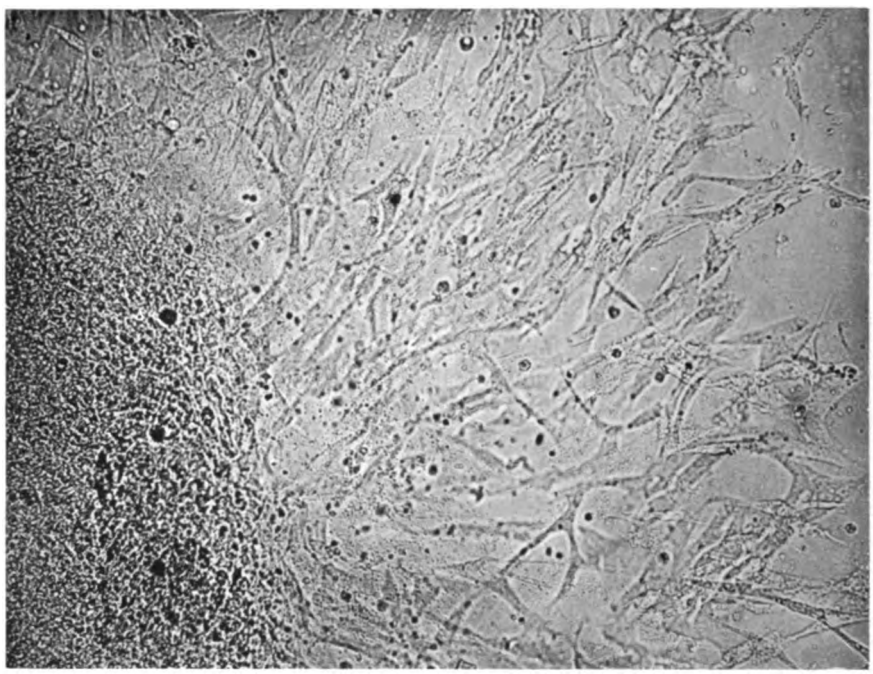

Fig. 1.—The living cells which had grown from a fragment of the body wall of a 5 day old chick embryo in a medium consisting of 1 part of plasma and 1 part of isotonic salt solution, 0.9 per cent.

This inhibition is preceded by a short period of activity. The typical effect on the cells is shown in Figs. 1 and 2. The first (Fig. 1) is a control culture showing the usual growth of cells and their typical spindle-shape form. The second (Fig. 2) is a culture in plasma plus asparagine, showing the cells rounded off and beginning to undergo dissolution.

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We do not wish to draw too extensive conclusions from these experiments, but we believe that the toxicity of α-amino-acids towards growing cells has been shown beyond a reasonable doubt; on the other hand, we have found that compounds of higher molecular weight, namely, the peptones of egg-yolk and proteins, are non-toxic. This toxicity depends upon the concentration and the time that the cells are exposed to their action. As these factors are reduced, the toxicity is decreased. In this respect, these substances are similar to all cell poisons.

Fig. 2.—The degenerated cells which had grown from a fragment of the body wall of the embryo used in the culture in Fig. 1 in a medium consisting of 1 part of plasma and 1 part of an isotonic solution of asparagine.

Applying these results to the work done on the intravenous injection of digestion mixtures, we believe that we have found a reason for the death of the experimental animals when the hydrolyzed proteins were injected too rapidly. Buglia * found that large amounts of α-amino-acids could be injected into the circulation without causing deep-seated

* Buglia, G., *Z. Biol.*, 1912, XVIII, 162.

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changes in the renal and intestinal functions, provided they were injected slowly enough; in fact, that enough of these mixtures could be injected in this way to cover the nitrogen consumption of the body. This injection, however, was always accompanied by an α-amino excretion through the urine and an increase of the peristalsis of the intestine, with resultant liquid stools. As is well known, a sudden great concentration of these substances in the blood of an animal causes death. These results agree with our findings.

Folin and Denis * demonstrated the fact that α-amino-acids probably pass into the circulation through the intestines. Van Slyke and Meyer,† by means of Van Slyke's ‡ nitrogen method, have practically proven this, and Abel, Rowntree, and Turner, § and Abderhalden ‖ have lately succeeded in obtaining α-amino-acids in crystalline form from the blood. Van Slyke and Meyer ¶ have shown that the tissues take up α-amino-acids to a certain point, but that after this the limit of saturation is reached. This is not so in the liver, which continually desaturates itself by metabolizing the α-amino-acids that it has absorbed and consequently maintains indefinitely its power of removing them from the circulation, as long as they enter it no faster than the liver can metabolize them. Marshall and Rowntree ** have shown that there is an increase of the α-amino-acid concentration in the blood after injuries to the liver, which have caused deep-seated anatomical changes. Our experiments prove that tissue cells in general are unable to live in the presence of any great concentration of these acids.

At the present time we do not feel able to give an explanation of the significance of this evident toxicity. However, the fact in itself seems to indicate that we should expect stimulation from a certain increase of the α-amino-acid concentration in the body, or the concentration of any one of the acids, whereas a greater increase would lead to marked disturbances of the metabolism.

* Folin, O., and Denis, W., *J. Biol. Chem.*, 1912, XII, 141.

† Van Slyke, D. D. and Meyer, G. M., *J. Biol. Chem.*, 1912, XII, 399.

‡ Van Slyke, D. D., *J. Biol. Chem.*, 1911, IX, 185; 1912, XII, 275.

§ Abel, J. J., Rowntree, L. G., and Turner, B. B., *J. Pharm. and Exp. Therap.*, 1913-14, V, 275, 611.

‖ Abderhalden, *Z. physiol. Chem.*, 1913, LXXXVIII, 478.

¶ Van Slyke and Meyer, *J. Biol Chem.*, 1913-14, XVI, 213.

** Marshall, E. K., and Rowntree, L. G., *J. Exp. Med.*, 1915, XXII, 333.

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THE SIGNIFICANCE OF THE LUNULA OF THE NAIL.

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A structure, the significance of which has always been described by a series of different answers in modern text-books of anatomy, is the lunula of the nail. This is a small, sharply circumscribed opaque area, which is visible near the root of the nail of many persons. Toldt assumed that the greater opacity of this region is due to the fact that the nail is covered here by a layer of matrix, the cells of which are undergoing active division. Unna expressed the opinion that the opacity is conditioned by the existence in this region of keratohyaline (onychogenic substance). Ranvier has given a similar explanation (quoted from Poirier and Charpy, *Traité d'anat. hum.*, Paris, 1901). He ascribed it to the existence of onychogenic granules which fill the cells of the rete mucosum. V. Brunn, on the other hand, ascribed it to the fibrous structure of the cells undergoing keratinisation in this region of the nail.

Although these particular explanations have for a long time appeared to be inadequate, it is of interest that no one, so far as the author has been able to determine, has attempted to study more carefully the peculiarities in the structure of this region. The fact that the lunula is marked off sharply from the remaining portion of the nail is a direct argument against several of the above explanations. Again, the large number of nails which one sees removed in the dispensary do not show that portion of the nail corresponding to the lunula to be more opaque than the surrounding parts.

During the last few months a careful study of the structure of the nail and its environment has been undertaken for the purpose of establishing, if possible, some of those conditions which regulate its continuous growth throughout the life of the individual. This study has been planned to include not only a careful investigation of the morphology, histology, and the development of the nail, but also a detailed study of its connective-tissue support and vascular supply, as far as

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they apply to the solution of the problem in question. It represents a continuation of those studies of the mechanism of cellular growth which have been carried on for some time in the laboratory by means of the tissue culture method.

It was during the course of the early part of this study that the author noticed certain peculiarities in the structure of the nail in the region of the lunula which have appeared to be important in conditioning its opacity. Since the lunula itself has a certain clinical as well as a morphological importance, and since these particular peculiarities of structure have hitherto been little emphasized in anatomy, although probably very significant as a part of the general mechanism of the growth of this structure, it became of importance to report them in a separate communication.

The nails of the hands of five persons have now been studied. They have included those of two adult white men, an adult negro woman and two white children. Lunulæ were noted at the base or uncovered portion of the body of the nails of all the fingers of the white men, and on the thumbs of the children. None was seen on any of the fingers of the negro woman before the epitrichium had been removed. When the epitrichial layer is lifted, however, the sharply defined opaque lunular zone is seen. It was present in all the fingers of this woman.

A number of these fingers were dissected at once. Others were fixed in formalin, dehydrated and decalcified. The blood-vessels of a number of the fingers were injected with India ink. These fingers were likewise fixed in formalin, dehydrated and decalcified. The fingers which had been fixed were either embedded in colloidin, sectioned and stained, or they were sectioned free-hand, examined at once, and later after they had been cleared. All the unfixed fingers were hemisected along the median sagittal plane. This was accomplished by first cutting through the nail and the soft parts with a sharp knife, the bone being later cut through with a fine saw.

In every one of these fingers examined it has been noticed that the matrix of the nail underlying the lunula is not firmly adherent to the connective-tissue stratum. Throughout the whole lunular area, the two layers do not apparently adhere but lie only in contact with each other. The slightest distortion of a sagittal section of the finger leads to the separation of these two layers. The open space thus formed is sharply circumscribed. It extends from the tip of the root of the nail, at which point the matrix is firmly adherent, to a line that corresponds to the

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distal margin of the lunular zone. Beyond this line and over the whole body of the nail the matrix is firmly adherent to the underlying connective-tissue layer (Figs. 1 and 2).

The connective tissue underneath the lunula is peculiar in structure. The fibrils near its outer edge run parallel to the lower margin of the nail matrix. They form a dense boundary layer or sheath. The con-

FIG. 1.—A thick sagittal section of the finger of a white man. A piece of paper has been passed through the opening between the matrix and the connective tissue.

FIG. 2.—A thick sagittal section of a finger of a white man which has been fixed, dehydrated and decalcified. The open space between the matrix and the connective-tissue layer is readily discernible in the area corresponding to the lunula.

nective tissue here is not vascular. The capillaries are reduced to a single or double layer, which lies close to and on the surface of this layer of connective tissue. The underlying portions of the connective tissue contain few capillaries.

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The matrix is also peculiar in this region. Its lower margin is in most parts straight. One sees very few indentations or papillary extensions into the underlying connective tissue. This is in sharp contrast to the outer pink portion of the nail body. Here the matrix is indented both longitudinally and traversely by connective-tissue papillæ. The connective tissue in this region is also strikingly different from that of the lunula. It contains many vertically placed fibrils, which end directly at the edge of the epithelial cells of the matrix. They adhere closely to these cells or a basement membrane. The papillæ, as well as the neighboring portions of the connective tissue, contain large numbers of capillaries. They form a dense network which fill the papillæ and neighboring parts of the connective tissue. This dense capillary network is continuous with that of the lunular portion, the change from one form into the other taking place gradually under the distal margin of the lunula.

A number of the nails of the fingers examined have been removed by stripping them back from their outer tip. By this procedure it is possible to remove the nail with the matrix of the lunula attached to it. Throughout the body of the nail the matrix is invariably torn. In none of the nails thus removed has the lunular portion been found to be more opaque than the remaining portions. Quite the reverse, this area is frequently more translucent. In a number of the nails which had been previously fixed, dehydrated and decalcified, the tip of the root did show a definite opacity. In none of these cases, however, is this opacity seen as far forward as the distal margin of the lunular area. It fades and gradually disappears a short distance distal from the tip of the root. Furthermore, this opacity is not noticed in all the fixed specimens.

From these latter observations it seems evident that the opacity of the lunula is not conditioned by any peculiarity of the structure of the nail itself or of its matrix. Moreover, that the decrease in the capillary bed of the lunular area is not wholly, if at all, responsible for the opacity may be deduced from the fact that its change in density at the distal margin of the lunula is never as abrupt as the boundary line of the lunula demands. Further proof that this peculiarity does not play any important rôle in conditioning the opacity is given by comparing the appearance of the lunular area with a portion of the body from which the blood has been removed by pressure. The lunula has a

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definite opacity, whereas that portion of the body from which the blood has been removed has a greyish translucency.

In the absence of other possibilities, the author has been led to believe, therefore, that the lunular opacity is the result of a reflection of the light at the surfaces of the junction of the matrix and the connective tissue of this portion of the nail. In the outer portion of the nail where the matrix adheres closely to the underlying connective tissue, the light is transmitted directly to the capillary bed, giving it its characteristic pink color, whereas in the region of the lunula the well-formed, non-adherent surfaces of both the connective tissue and the matrix reflect the light. More direct proof for this assertion may be readily obtained by pulling a portion of the body of the living nail loose from the connective tissue, thus forming such a surface in this region. During the last few weeks the author has been performing work which has led to the production of this injury. In each instance when it has occurred, the detached portion has shown an opacity quite indistinguishable from the opacity of the lunula of the same finger. It is of interest, however, that unless the injury is extensive, the nail will again, after a few hours, become adherent and assume its former pink color.

The decrease in the capillary bed of the lunular area has been described. No one, on the other hand, as far as the author has been able to determine, has described the peculiarity of adhesion between the matrix and the connective tissue in this region, or the relation of this peculiarity in structure to the lunular opacity. It will be of further interest to ascertain whether many of the pathological opacities of the nail are not the result of similar changes, to study more carefully the conditions which lead to the adhesion of the matrix, in outer portion as contrasted with that of the lunular zone, and the general changes in the connective tissue and in the arrangement and density of the capillaries in these two regions. The nail is one of those peculiar parts of the body which continues to grow throughout the whole life of the body. A more careful investigation of its general structure and the chemical and physical changes which accompany its growth may lead to many facts of importance for ultimately ascertaining the conditions that bring about and regulate the growth of other body structures.

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THE OXYGEN PRESSURE NECESSARY FOR TISSUE ACTIVITY.

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The ordinary plasma culture is sealed into a very small chamber of a hollow ground slide. The cultures are made by placing small fragments of tissue into layers of liquid coagulable plasma on the surface of a cover-glass. The cover is placed over the hollow ground slide so that the tissue and the plasma hang in the hollow chamber. It is sealed to the slide with vaseline and paraffin.[1] From the air chamber the cells obtain the oxygen necessary for their activities, and it has been of interest that in such a small chamber the cells may continue to grow actively for several days. This observation had already led to the belief that these cells may grow in very low concentrations of oxygen. This belief was further substantiated by the fact that the renewal of the air had little or no noticeable effect on the growth or activity of the cell.

That the oxygen essential for activity in the culture is derived from the air chamber was determined by placing two small glass tubes under the cover and replacing the air in the chamber by hydrogen and sealing. No growth took place in these cultures.

A considerable amount of work has recently been done to determine at ordinary atmospheric pressure the per cent of oxygen necessary to maintain a flame as well as to maintain the life of organisms. Clowes[2] and Loevenhart[3] noted that alcohol ceases to burn in an atmosphere containing 15 per cent of oxygen. The latter author noted that ether and Madison (Wisconsin) illuminating gas ceases to burn at 13 per cent, while hydrogen continues to burn until the atmosphere contains 6.6 per cent of oxygen.

With the animal, conditions are different. Loevenhart found rabbits would live in an atmosphere containing 3.5 per cent of oxygen, but that they died when this was reduced to 3 per cent.

In the present series of experiments, an attempt has been made to determine the effect of pure oxygen and various partial pressures of

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oxygen on the growth of the cells *in vitro*. Although at the present time the apparatus is still not perfect, and a few of the results given here have a slight error, it seems that in their present form they warrant publication.

Materials and Methods.

The gas and mixture of gases tested have been kept at atmospheric pressure. The partial pressure of oxygen has been lowered by diluting it with nitrogen. The culture chambers used have a large air space 40 to 60 times that of the ordinary culture.

To make these determinations, it was necessary to prepare pure oxygen and nitrogen and to devise a culture from which gases could not diffuse. The cultures, therefore, were made in sealed glass chambers.

The Culture Chamber.—The culture chamber, as shown in Fig. 3, *a*, is blown from soft glass tubing ¼ inch in diameter. In place of the cover-glass used in the ordinary cultures, one small part of one side of the tube is blown out, made very thin and flattened. Opposite this place the tube is again blown out and flattened. This latter flat surface forms a base for the culture and allows free transmission of light, which is essential for examining the cultures under the microscope. On each side of the central portion the tube is constricted so that it can be easily sealed with a small flame. Beyond this point, it is left full size, but corrugated to allow a rubber tube to be tightly fitted. These culture chambers are easy of construction, and they are made in the laboratory as they are needed.

The culture chambers thus prepared are boiled in soap and water, left to soak several hours in H_2SO_4, and then rinsed in tap-water and distilled water. They are steamed for several minutes to remove soluble substances in the glass and are then sterilized by dry heat.

Oxygen.—The oxygen is prepared by dissociating a 1 per cent aqueous solution of H_2SO_4 with an electric current. This method of preparing oxygen is well known. The particular apparatus used works automatically and is shown in Fig. 1. The current used is D. C. 110 volts, which has been passed through a resistance of from 1 to 4 16-candle power carbon lights. The apparatus is made automatic by interrupting one of the wires with a platinum-pointed switch operated by a float.

Oxygen prepared in this manner is something over 99 per cent pure. It contains, however, a small amount of ozone, hydrogen and water

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vapor. Since the ozone attacks organic matter and may become injurious, especially if rubber tubing is used at any point, the gas, before being used, is bubbled through olive oil. To remove any traces

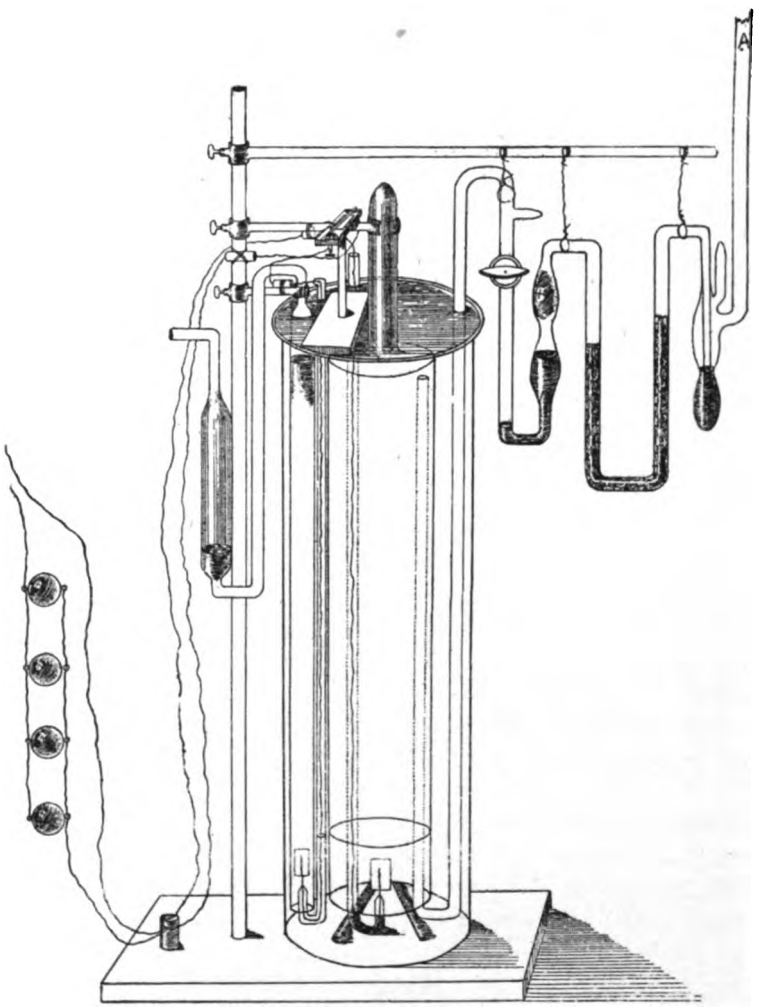

FIG. 1.—An automatic oxygen-hydrogen generator.

of acid, it is further passed through a tube containing soda lime and bubbled through a strong aqueous solution of KOH (40 per cent). No rubber connections are used in any part of the apparatus. The apparatus is continuous except for one joint which is ground glass.

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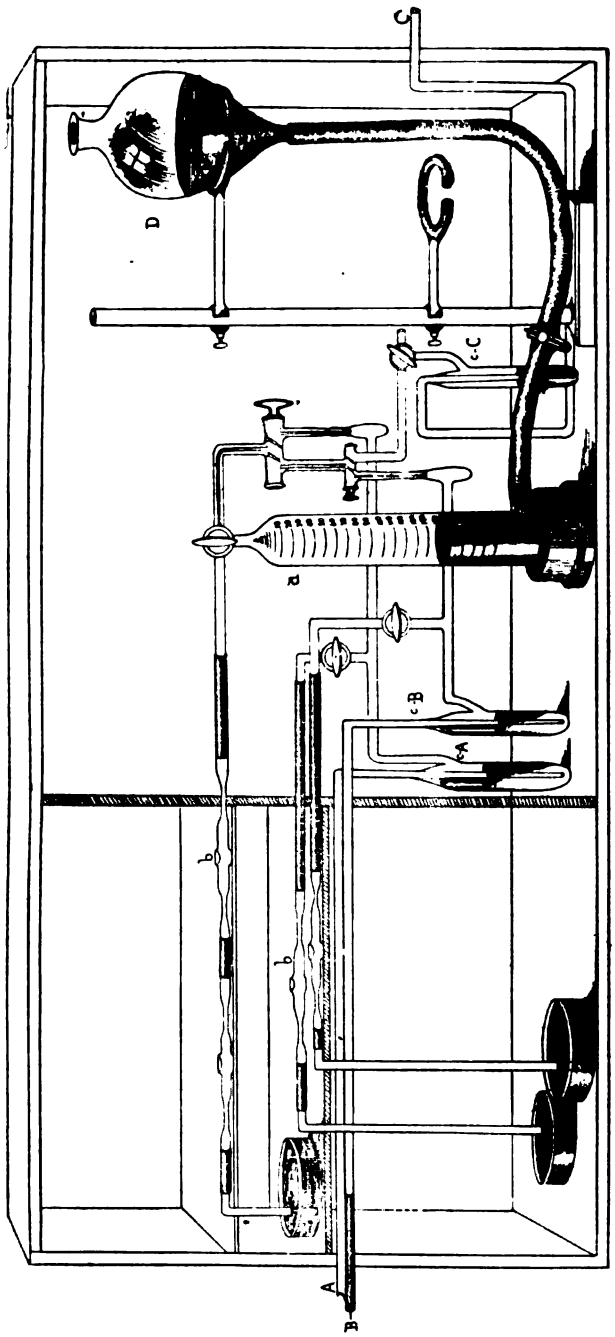

FIG. 2.—Gas conducts, washing cylinders, measuring cylinder and cultures within the incubator. *A*. Tube carrying oxygen. *B*. Tube carrying nitrogen. *c-A*. Oxygen washing cylinder. *c-B*. Nitrogen washing cylinder. *b*. Culture chambers.

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Nitrogen.—The nitrogen is commercial. It contains about 2 per cent of oxygen, which is removed by bubbling the gas through several long cylinders containing pyrogallol and potassium hydrate. These are mixed according to the proportions given by Hempel (page 149).[4] Potassium hydrate, 120 gm., is dissolved in 80 c. c. of water. To this is added 5 gm. of pyrogallol dissolved in 15 c. c. of water. Hempel states that no CO is formed when a solution of these proportions is used. To insure against this possibility, the gas is bubbled through two cylinders containing Sandmeyer's solution (Hempel, page 203).[4] It is then passed through a tube containing soda lime and bubbled through a strong solution of KOH, 40 per cent.

Preparation of Cultures and Tissues.—For these experiments fragments of heart muscle and skin of chick embryos, from 5 to 16 days of age, have been used. The medium is plasma prepared from the blood of adult chickens. When thin layers of plasma are placed in these large

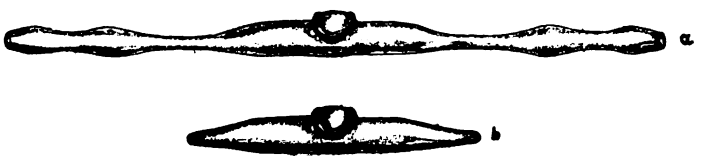

FIG. 3.—*a*. The complete culture chamber.
b. The sealed culture chamber.

culture chambers, some slight evaporation may take place. To prevent this from causing an injurious hypertonicity, the plasma before being used is diluted .1 with sterile distilled water. Fragments of both heart muscle and skin are planted in each culture.

It is impossible to prepare these cultures in the ordinary manner. The method used has been to mix together quickly outside four or five pieces of tissue with a drop of liquid plasma. The plasma and tissue, then, before the plasma clots, are sucked into the end of a long, slender pipette, which may be passed into the culture chamber and the drop of plasma containing the tissue fragments deposited on the thin, flat surface which has been prepared for it (Fig. 3, *a*). The culture chamber is then gently shaken so that the drop of plasma spreads in a layer no greater than $\frac{1}{2}$ mm. in thickness, and the tissue fragments become scattered in this layer over the surface of the glass. The fragments of tissue are 1 mm. or less in diameter.

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As soon as the plasma has clotted, the chambers are turned over so that the culture hangs into it. The side walls of the culture chamber are moistened with sterile water, so as to further prevent as far as possible any evaporation of the culture medium. In each experiment, one, two or three cultures are used. Besides these in most instances, three control cultures are also prepared. The air in one of the controls is replaced by nitrogen gas. In the other it is replaced with pure oxygen, the third is sealed at once and acts as an air control. This last culture, which contains air, controls the tissue and plasma as well as the activity observed in the cultures where pure oxygen gas is being tested, but it does not control any possible toxic substances in the nitrogen. An attempt to partially control this was made by substituting air for oxygen in several experiments. It was possible by this means to use for the very low dilutions of oxygen a quantity of nitrogen, which had been proven not to be toxic in those cultures where a higher partial pressure of oxygen had been tested and an active growth of cells had been observed. The cultures prepared have shown no evidence of toxic substances in the nitrogen gas.

Since it is essential for all these determinations that the gases used be saturated with water vapor at the temperature at which the cells are grown, the measuring of gases and the filling of the culture chambers with the gas to be tested is made always in the incubator. The arrangement of the apparatus within the incubator is illustrated in Fig. 2. The oxygen and nitrogen are passed through slender glass tubes *A* and *B*, respectively, across to the middle of the incubator where each is bubbled through cylinders containing distilled water, *c-A* and *c-B*, respectively. From the water cylinders the gas passes into T-Tubes, one arm of each of which is open and fitted with a stopcock. To this open arm the cultures in which the pure gases are to be tested are attached. The other arm passes to the measuring cylinder. The measuring cylinder is arranged so that not only these but other gases may be tested. The gases are measured over mercury. In order to keep them saturated, a thin layer of freshly boiled distilled water is run over the mercury surface before they are admitted. The measurements are made at the temperature of the incubator. The measuring cylinder is fitted at the top with a 3-way cock. One arm of the cock is open, and to this the culture chamber (*b*) is attached by means of a rubber tube.

The air in the culture chambers is replaced by pure gases or a mixture of gases in the measuring cylinder by allowing these gases to

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pass rapidly through the culture chambers at regular intervals during a period of one or two hours. The free open end of the culture chamber is fitted with a rubber tube and a piece of glass tubing. The free end of the latter is passed just underneath the surface of water contained in a small dish. After the air in the chamber has become entirely replaced by the gas to be tested, and the medium of the culture may be assumed to have become saturated with this gas at atmospheric pressure, the culture chambers are sealed by fusing the small constricted portions of the tube, Fig. 3, *b*. The cultures are left in the incubator and examined periodically under the microscope, which is in a warm box. The maximal growth attained is recorded.

The measuring cylinder used in these experiments is a large one, and the general method of measuring the gases is not very accurate. For this reason the measurements were in several instances checked by removing a sample of the gas and determining its oxygen content by the Haldan method. The pure oxygen and nitrogen gases were also tested by the same method (see table).*

TABLE I.

Date.	Partial Pressure of O. and N.		Corrected % of O. by Haldan method.	No. of experiments.	Av. growth of experiments.	Av. growth of control (air).	Barometer.	Partial pres. of O. at 39° C.
	No. of c.c. of O.	No. of c.c. of N.						
Various times..	100	0	100.0*	50	++++	++++	764.1*	712.1*
Various times..	80	20	.....	8	++++	++++	.....	.....
Various times..	60	40	.....	6	+++	+++	.....	.....
Various times..	40	60	.....	7	++++	++++	.....	.....
Various times..	20	80	.....	15	++++	++++	.....	.....
Various times..	15	85	.....	6	++++	++++	.....	.....
Various times..	12	88	.....	4	++++	++++	.....	.....
Various times..	10	90	.....	6	++++	++++	.....	.....
June 2, 1916 ...	9	91	.....	1	+++	+++	.....	.....
Various times..	8	92	.....	6	++++	++++	.....	.....
Various times..	7	93	.....	1	++	+++	.....	.....
June 21, 1916 ..	6	94	.....	1	+	++++	.....	.....
June 28, 1916 ..	6	94	.....	2	+	+++	.....	.....
Dec. 11, 1916...	6	94	.....	1	0	++	.....	.....
Dec. 12, 1916...	6+	94—	6.6	1	+	+++	745.	45.6
Dec. 19, 1916...	5+	94+	5.63	1	0	+++	760.	40.66
Dec. 14, 1916...	5	95	5.0	1	0	++++	764.1	35.6
Various times..	5	95	.....	3	0	+++	.....	.....
Various times..	4	96	.....	4	0	+++	.....	.....
Various times..	0	100	0.40*	50	0	++++	.....	.....

* These figures represent but one determination made in the series, but since the other experimental conditions were constant they are representative of the series.

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It is also evident that in all these cultures another slight error must have resulted from sealing the tube and temporarily heating the air in the tube. This would make the actual pressure somewhat less than that recorded.

Discussion and Conclusions.

Results from the experiments are given in the accompanying table. Tissues of chick embryos grow somewhat better in the spring and summer than in the winter. In the first column, the dates of the experiments are recorded. The growth is recorded in terms of the area of new cells which form about the fragment. Since there is no absolutely accurate method of measuring this it is indicated by the relative term, +. In many cultures the cells grow in a single plane; in others they grow in several planes, and the density of the growth is not the same in one culture as in another.

As indicated by the corrected readings of the per cent of oxygen in the gaseous mixtures (column 4 of the table), many of the readings in column 3 are probably slightly higher than the table indicates.

Including these possibilities of inaccuracy in the measurements, it is quite evident, however, that certain definite conclusions may be drawn.

1. Cells may grow in an atmosphere of pure oxygen.

2. The growth in an atmosphere of pure oxygen, although often slightly more rapid, is not greater than the growth in a partial pressure of oxygen no more than 9 or 10 per cent.

3. Although the growth becomes less when the partial pressure of oxygen is lower than 9 or 10 per cent, very evident growth activity is seen in an atmosphere where the partial pressure of the oxygen is as low as 45.6 mm.

4. A method has been devised which in its full analysis will allow one to study in more detail many of those conditions which regulate oxidation in tissue cells and to study conditions which regulate oxygen pressure in the tissues.

These results have become of interest in that they show that the activity of the cells within the cultures is little influenced by changes in the oxygen concentration or partial pressure when it remains above a certain amount.

Again, they are interesting in that the lowest partial pressure of oxygen in which growth takes place is about the same as the venous

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oxygen pressure of mammals. The author does not know the venous oxygen tension of chickens. In the light of these facts an attempt is now being made to determine the venous oxygen tension of chickens, to study the effect of the addition of various substances to the plasma, and to measure with greater accuracy the lowest partial pressure of oxygen in which the cells may not only grow, but show other forms of activity.

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5. The author is indebted to Mr. H. L. Higgins, of the Department of Pediatrics, for making these determinations.
6. During the period of the development of the method, the cells were found not to grow in pure oxygen. The gas attacked the rubber tubing used in connecting the cultures. The medium in the culture became orange-red in color. This gas gave a definite test for ozone. It was not until the gas had been passed through olive oil that the results reported in the paper were obtained. Whether the ozone attacks the culture medium, liberating toxic substances, or whether it attacks the cells, was not determined. From the disintegrating rubber tubing SO_2 was liberated. The failure of growth may have been due to the presence of SO_2.

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THE FUNCTIONAL RELATION OF INTERCELLULAR SUBSTANCES IN THE BODY TO CERTAIN STRUCTURES IN THE EGG CELL AND UNICELLULAR ORGANISMS.*

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It has been shown that whether an embryonic heart muscle cell in a tissue culture grows and divides, grows to form a syncytium, differentiates, contracts rhythmically, or remains inactive, depends upon the particular kind of environment into which it is placed. Many of the peculiarities of the environment essential to each form of activity have been described, and evidence has been presented to show that these various activities are not the result of an organization contained within the cell, but that they are the result of differential changes of the surface tension of these cells. Each form of work and the structure peculiar to each form of work is the result of a specific kind of change. The changes in the surface tension are brought about and maintained by an organization in the environment, external to the cell, but influenced by the cell, as any phase of any physical chemical system of this kind is influenced by other phases.

These experiments indicate that the cells of the body differ from egg cells and many unicellular organisms, in that they do not possess the total organization necessary for their activity, but depend in part upon structures external to them. In the light of this fact it became of interest to compare the structure of the egg with the structure of the organization peculiar for the growth and the mitotic division of the body cells. It seemed evident that by this method one could determine definitely the true significance of many of the structures peculiar to the egg. What could be applied for the study of the egg cell could be applied also for the study of many unicellular organisms.

In the tissue culture the nutrient materials necessary for growth of the cells come from the tissue fragment. The cells that grow and

* Read before the Association of American Anatomists, at New Haven, Conn., Dec. 28, 1915.

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divide are those cells which are passively moved outward into the medium and come in contact with the surface of the substance which covers the medium and against which they flatten out. Growth, as seen in the culture, has been considered a specific differential surface tension reaction between the cell and specific substances liberated by the cells of the fragment.

The cells of the body one may readily consider as comparable to the protoplasmic portions of the egg. These facts lead to the question whether the important factor in the organization for growth and division in the egg is not to be found in the particular relation of the protoplasm to the yolk. In a large number of the eggs the protoplasmic portion lies at the surface of the yolk, and in no variety of eggs does one find the protoplasmic part directly in the center of the cell. This analogy between the organization suitable for growth in the cultures, growth of simple protoplasmic elements, and the general organization of egg becomes, therefore, of interest.

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STUDIES ON THE GROWTH OF CELLS.

THE CULTIVATION OF BLADDER AND PROSTATIC TUMORS OUTSIDE THE BODY.

By MONTROSE T. BURROWS, M. D., J. EDWARD BURNS, M. D., and YOSHIO SUZUKI, M. D.

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Although numerous workers have attempted to grow human tumors from different parts of the body, the cultivation of bladder and prostatic tumors has not been undertaken up to the present time. Cellular activity has been observed in only a limited number of the cultures of human tumors which have been tested, and those which have been observed to grow have shown few peculiarities which have aided in a better understanding of the conditions which initiate or regulate the growth of these cells.

During the last few months we have studied cultures from 12 tumors of the bladder and the prostate. The method, in brief, has consisted in placing small fragments of the tumor tissue (1 mm. in diameter) in a layer of medium (0.5 mm. in thickness) on the surface of a coverglass, and inverting over this a hollow ground slide, sealing it in place with vaseline and paraffin. The culture thus prepared was incubated at 37° C.

The media used have been plasma prepared from the blood of the patient from whom the tumor was removed, plasma from the blood of normal individuals, and a medium consisting of agar, .25 per cent, dissolved in isotonic sodium chloride, or isotonic sodium chloride and ascitic fluid. No difference was noted in the cellular activity in the cultures whether the plasma used as the medium was obtained from the first or the second source and the activity was as great in the agar as in the plasma.

Of the 12 tumors used for these cultures, seven were clinically malignant bladder papillomata; one, a benign bladder tumor; two, benign hypertrophy of the prostate; and two prostatic tumors, each of which showed in one portion typically benign hypertrophy, the other parts being carcinomatous. Besides these, one series of cultures of normal bladder epithelium was also tested. Of the seven malignant

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tumors cultivated, one only failed to show cellular activity in the first 20 hours. This tumor had been removed after the application of a strong solution of cocaine. The cultures of the benign tumor, on the other hand, have shown no cellular activity either in the first or second transplants. The general structure of this tumor is illustrated in Fig. 1. It is a benign polyp.

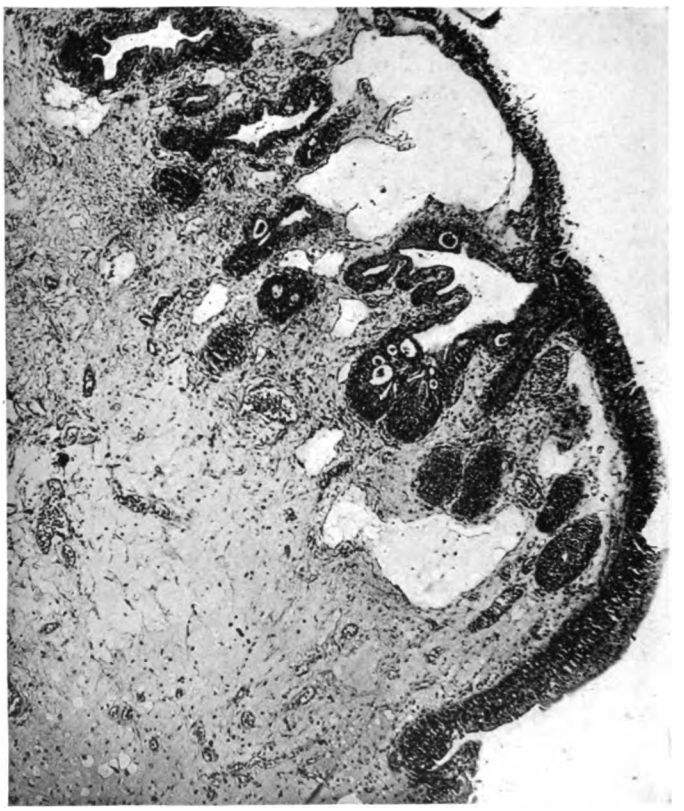

FIG. 1.—A section of the benign polyp, fragments of which were used for cultures.

All the cultures of the bladder tumors were infected with bacteria. However, before the time that the bacteria became very numerous, the tumor cells showed activity except in the instance noted above. The type of this activity is shown in the case of Tumor A11 (Fig. 2) in Figs. 3 and 4.

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A number of the fragments from these cultures were transplanted at the end of 20 hours from the first medium into a fresh drop of the same medium. The plasma clots were liquefied in the original cultures and the transplants very soon after they were incubated. The liquefaction was slightly more rapid in the original cultures than in the

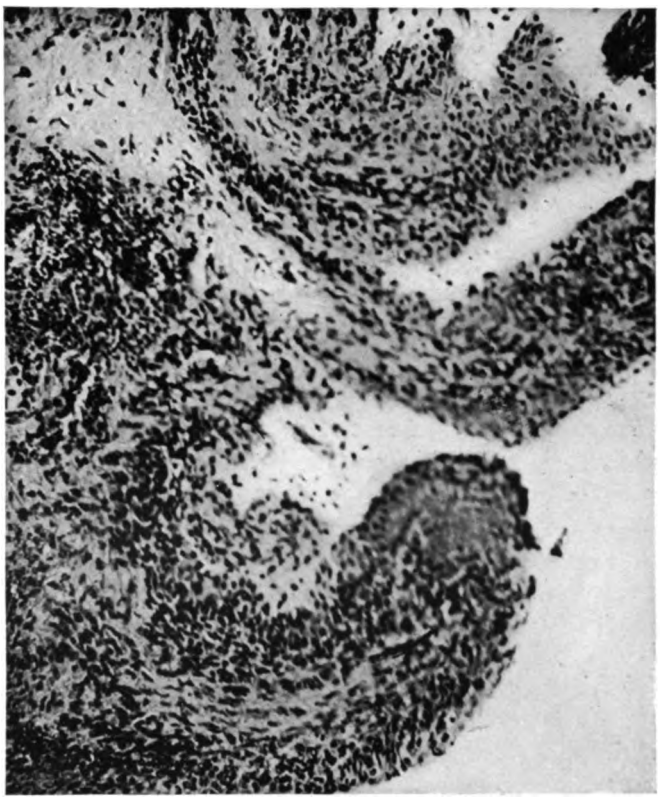

Fig. 2.—A section of the malignant bladder papilloma, fragments of which were used for cultures (Figs. 3 and 4).

transplants. It is impossible to say to what extent the bacteria aided this liquefaction.

This liquefaction was also noted by Carrel and Burrows [1] in cultures of human tumors and human tissues. The cells failed to show activity in a large number of instances. It was thought that this failure was the result of the liquefaction of the clot or the destruction of the solid

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medium necessary for the activity of the cells. They noted a moderate cellular activity, however, in a few of the cultures of giant-cell sarcoma of bone. The media had also undergone liquefaction about the fragments of this tumor. This in itself would make it seem that liquefaction of the plasma need not inhibit the activity of the cells.

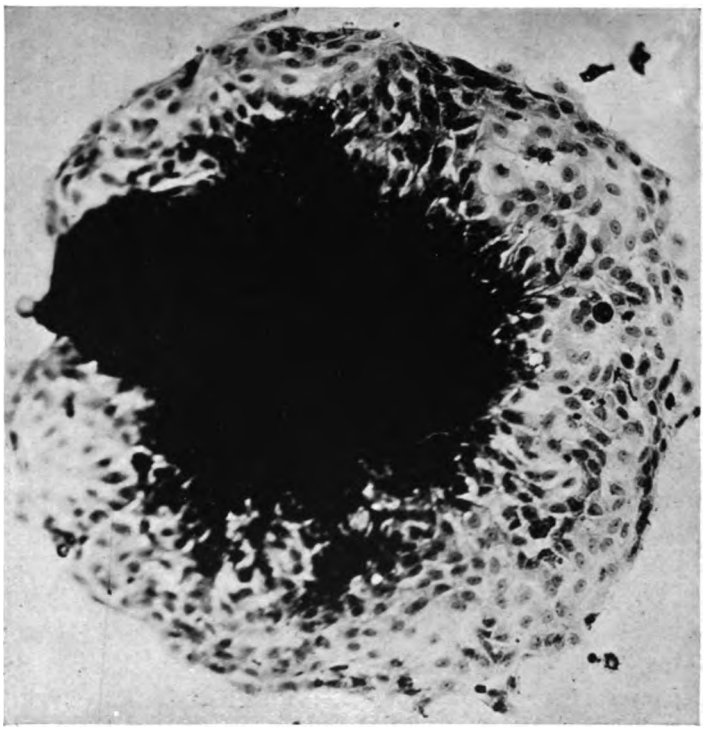

Fig. 3.—A tip of a papilla of a malignant bladder papilloma (Fig. 2) after 20 hours' incubation in a culture medium of blood plasma. The pedicle of the papilla is shown at the left side of the figure. The epithelial membrane surrounds the papilla, except at this point.

One of us (Burrows) during the last few years had again studied a number of human tumors as well as a number of normal human tissues at the General Memorial Hospital, New York City.[2] The tumors studied included a number of lymphomata, breast carcinomata. bone sarcomata, malignant tumors of the ovary, melanomata and a glioma. The normal tissues studied were fragments of connective tissue and

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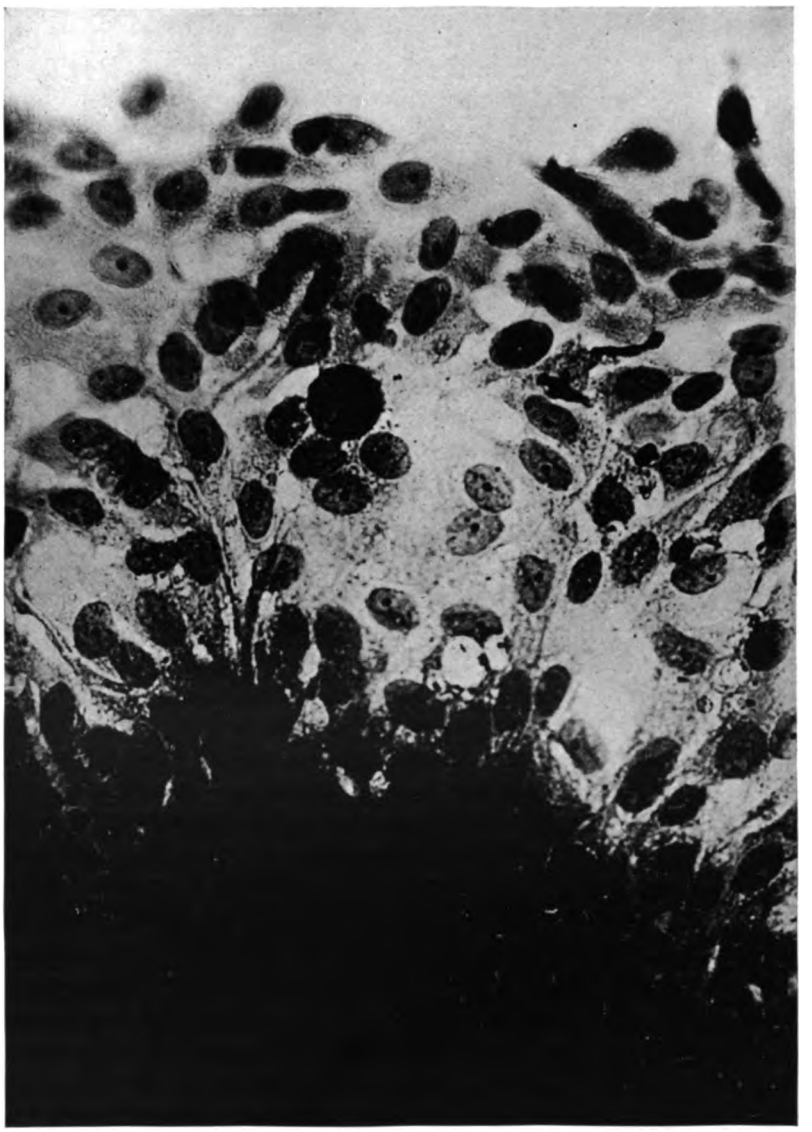

FIG. 4.—A high-power picture of a small area of the periphery of the zone of cellular activity shown in Fig. 3.

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arteries removed from normal men at operations for the repair of hernia. The plasma was liquefied about all the fragments of normal tissue which were studied, and a number of the fragments of the tumors. There were, however, certain tumor fragments which did not show this change. These were found among the lymphomata and the bone sarcomata. One ovarian carcinoma showed this change to a very limited extent. A further study of the normal tissue fragments has shown, however, that if the fragments were removed from the first medium at the end of the 20 or 24 hours (incubation at 37° C.) to a second drop of plasma, they no longer possessed this property of liquefying it, but a characteristic and often an active growth of connective tissue was noted about them. If they were removed at an earlier time, the plasma was again liquefied; when removed at a later date, no cellular activity was observed.

The growth of the cells and the changes in the medium were similar to those noted in the cultures of connective tissue of lower animals. The plasma-clots undergo contraction with the formation of sheets of fibrin, open fibrin networks or long, coarse fibrin fibrillæ, which radiate out from the fragments into the surrounding medium. The cells migrate out and grow along these fibrin formations. By the use of this method of replantation it was found possible to cultivate the cells of ovarian adenomata, several sarcomata, a glioma, and two melanomata. Whether the tumor cells themselves grew from the fragments of the melanomata could not be determined. The cellular activity observed may have been stroma-cell activity. Both the stroma cells and the tumor cells grew from the fragments of the other tumors. All the epithelial tumors failed, however, to respond by this method. The plasma was liquefied after each transplant until the cells were exhausted and dead.

This property of liquefying the plasma as shown by the epithelial tumors is not, however, peculiar to them. It is a peculiarity of many epithelial tissues. A piece of frog's skin liquefies the plasma for as many as eight transplants, or until the cells are dead. A large number of the ectodermal and endodermal tissues of animals have shown similar properties. The liver cells of a few chick embryos have, however, shown an exception to this rule. The plasma was not liquefied in the second transplant and the cells grew actively. Whether certain of the other glandular tissues might not show the same peculiarities has not as yet been determined.

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Maccabruni[3] studied fragments of uterine carcinomata and noted that the cells grew in a few of the cultures when the plasma prepared from the blood of a pregnant woman had been used as a medium. His success he assumes to be due to the particular selection of plasma. Other observers[4] working with Carrel have noted in later studies cellular activity in a number of cultures of human tissues and tumors. In these instances the plasma had not undergone a rapid liquefaction. They note differences in different plasmata, and that the addition of Ringer's solution may prevent liquefaction. Burrows planted fragments of each of a number of the tumors which he had studied in as many as seven different plasmata. These included plasmata prepared from the blood of normal men, normal women, women in the early and late months of pregnancy, and individuals suffering from chronic syphilis and tuberculosis. There was no definite and sharp relation noted between the growth or liquefaction and the plasmata used. In a few instances a plasma was used which killed the cells. This was noted in cultures when the plasmata had been prepared from the blood of patients ill with pneumonia. Although the number of these experiments was small they showed definitely that a large number of variations in the activity of human tumor and normal tissue in the plasma cultures are to be ascribed rather to variations in the tissue fragments than to variations in the plasma used.

Other general observations made on the growth of normal tissues would also tend to establish this view.[5] The energy-producing substances for the growth of these tissues has not been shown to come from the medium. The tissue culture in this regard is not comparable to an ordinary culture of bacteria. These substances, on the other hand, are probably derived from the tissue fragment and from the breaking-down of cells contained within it. The growth observed may be readily defined, therefore, as a simple transfer of materials from the cells within the fragment or in a less favorable environment to those on the periphery. Proof of this belief has been found in many observations. In plasma culture, growth and other forms of activity cease and the cells are exhausted after a few transplants. The sum total of the growth in the various transplants is less than the original mass, and it might well be considered as the original mass minus the energy of transfer. Again, cells may grow actively from fragments of tissue placed in a medium of simple isotonic sodium chloride, or in Ringer's solution, which contains no energy-producing substances.

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In a tissue culture an isolated cell will not grow. Isolated epithelial cells, lymphocytic and leucocytic cells show very little or no activity. Connective-tissue cells show movement. When isolated in a drop of liquid plasma they round off. After the clotting of the plasma and a variable latent period they are seen to send out processes, assume stellate or spindle shapes. They may migrate two or three cell-lengths. At this time they show vacuolation and exhaustion.

The growth of cells is seen only about fragments of tissues. When other conditions are equal, this growth is proportional to the size of the fragments. It is seen to take place actively only when the fragments are compact and about 0.3 or 0.4 mm. in diameter. This particular relation holds only up to fragments of 1 mm. in diameter. From fragments of this size the growth is maximal, excepting in cases where thin slabs are used.

The growth of connective-tissue cells is again influenced in the culture by the presence of muscle or epithelial cells within the fragment. If an active liquefaction of the clot does not proceed and prevent in a great measure the growth of the cells, the growth of the connective tissue is most extensive about fragments containing these cells. These more highly differentiated cells break down apparently at the expense of the connective-tissue cells.

A careful study of these cultures in serial sections, after a growth of cells has taken place, has shown the whole mass of cells in the center of the fragment to have deteriorated. In many instances they have become reduced to mere shadows.

Other studies have shown that the actively growing embryonal tissues grow readily in liquid media. This growth takes place, however, only when the fragments are brought into intimate contact with the surface of the medium and only when the culture medium is not agitated. Growth is most active when cellular and fragile fragments are placed in a small drop of medium spread in a very thin layer over the surface of a cover-glass. About each fragment, according to its content, is seen either a growth of mesenchyme cells or the formation of membranes or sheets of epithelial cells. These cells do not move out directly into the medium, but along or near the cover-glass or lower free surface of the medium. Previous to this growth, however, the lower surface of the medium in many of these cultures is seen to change. The surface becomes fixed, and currents cannot be set up easily.

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It is interesting that the cells do not grow directly in contact with the cover-glass, or directly in contact with the lower surface of the medium, but always in a plane just beneath these surfaces. If the same cells are broken loose from this apparent plane of contact and immersed in the liquid, they round off and show no further activity. If pushed back into this plane, they again flatten out in a passive fashion and may show active growth.

These observations show that growth takes place only along one plane in the culture. The passive flattening of the cells suggests that a surface exists here and that this surface must have been formed from the flowing out of substances from the fragment.

Although these facts had clearly shown that a change had taken place at the surface of the medium, and indicated that the food materials probably diffused along this surface, in only a very few cultures studied could one see that a definite layer of substance existed here. The refraction of the substance was quite similar to that of the underlying medium.

In the light of these observations a study of the bladder tumors became of interest. In all the cultures of the bladder tumors, malignant and benign, as well as the cultures of normal bladder epithelium, the plasma-clots underwent liquefaction. The failure of the growth of cells from the fragments of the benign polyp and normal bladder epithelium is not necessarily unique. Although actively growing embryonal tissues are seen to grow in liquid media, little or no cellular activity has ever been seen about fragments of normal adult tissues of either man or animals in these media. On the other hand, many of these tissues grow readily in plasma-clot.

The growth of the malignant bladder tumor cells in these cultures was preceded always by the formation of a definite membrane over the surface of the liquefied medium. In these cultures this membrane was homogeneous but quite easily seen. It contained a considerable number of granules; it was very tough. The surface that it covered could not be disturbed easily by shaking. It frequently formed over the lower surface of the medium as well as near the cover-glass. In many of these cultures the layer of medium was thick. It was along the surface of this membrane that the cells apparently moved outward from the fragment. In these cultures, as in the cultures of embryo chick tissue, with a few exceptions the line of demarcation between this surface zone and the underlying medium was not made out. Small fragments

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of tumor cells floating in the medium, coming in contact with it, flatten out.

As to the mechanism of the formation of these membranes, no direct observations have been made. They form generally very early in the life of the culture, often apparently during the liquefaction of the medium.

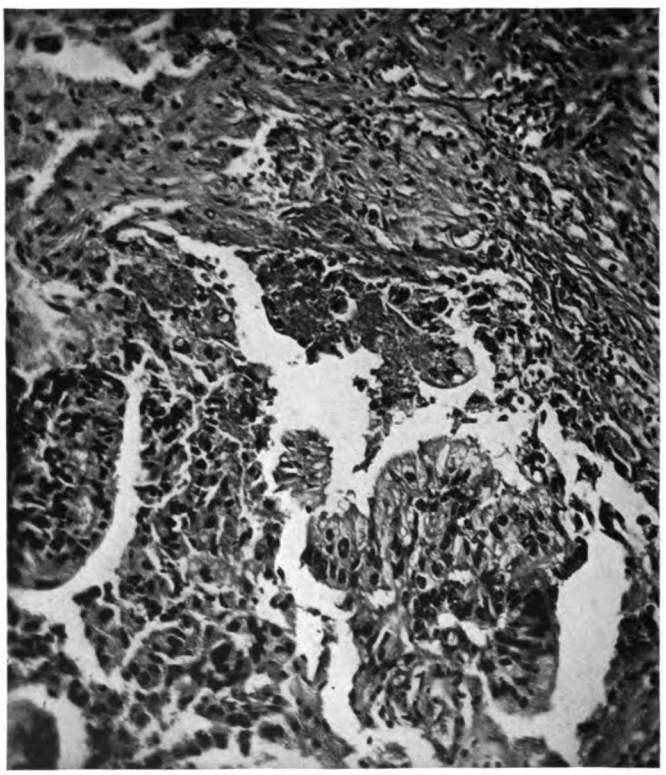

FIG. 5.—A section of the malignant portion of the prostatic tumor, fragments of which were used for cultivation.

In many of the cultures of bladder tumors the sheets of cells seen about the fragments form by a simple migration of cells from the fragment. In other cultures the area covered by cells is very large; too large to be accounted for by migration alone. Growth here must have taken place, although mitosis was not observed.

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Besides these cultures of fragments of bladder tumors, fragments were also taken from two hypertrophied prostates which contained carcinomatous areas. Membranes formed and the cells showed move-

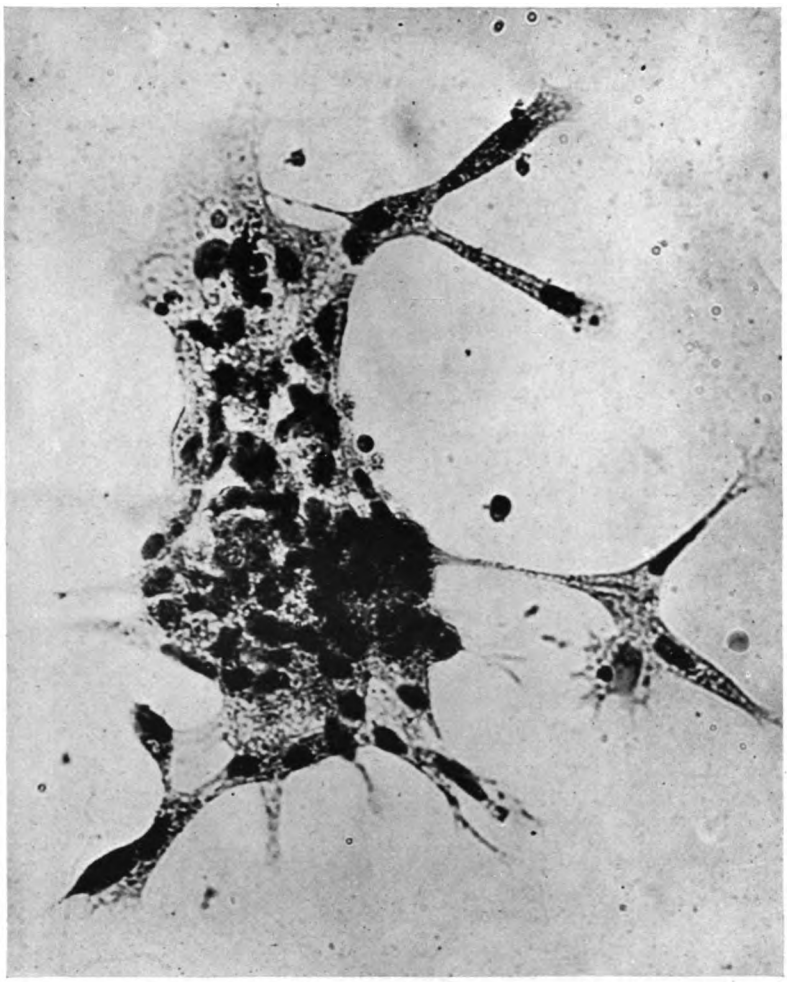

FIG. 6.—Migrating malignant prostatic tumor cells obtained from tumor (Fig. 5).

ment (Fig. 6) and slight evidences of growth about fragments taken from the carcinomatous portion of one of the prostatic tumors (Fig. 5). No change other than liquefaction was noted about the

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fragments taken from the benign portions. Cultures of fragments of other hypertrophied prostates have given the same negative results.

It was interesting in the case of the other hypertrophied prostate having carcinomatous areas, that no activity was observed about either the fragments taken from the carcinomatous or benign portions. This prostate had been treated with radium for four months previous to its removal.

Summary.

These observations have shown facts which may prove important for a better understanding of the conditions essential for the growth of body cells and the general structure of these cells. In none of the cultures of the benign tumors was any cellular activity noted; on the other hand, all of the cultures of the malignant tumors showed marked cellular activity excepting in the two instances above mentioned. This activity was observed in a large percentage of a series of cultures from each malignant tumor, and occurred in some of them as early as five hours and in all within 20 hours after their preparation. The facts indicate that this method may be important in determining the malignancy, in following the course of treatment, and in studying the biological properties of these tumors.

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THE STUDY OF A SMALL OUTBREAK OF POLIOMYELITIS IN AN APARTMENT HOUSE, OCCURRING IN THE COURSE OF AN EPIDEMIC IN A LARGE CITY.

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The paper which follows is the study of a small outbreak of poliomyelitis occurring between September 15 and October 1, 1916, in a large apartment house, occupied by 30 families, situated in the outskirts of a large city. Wickman[1] pointed out that the outbreaks of poliomyelitis in the small Swedish villages were the most fruitful sources of knowledge concerning the mode of transmission of the disease. The outbreak of poliomyelitis in the X House seemed to offer in a similar way an exceptional opportunity for study, for the children in it formed a small community of their own, fairly well isolated from the rest of the city.

The outbreak of poliomyelitis at the X House is, however, interesting apart from the standpoint of its epidemiology; for of the 8, very possibly 10, children affected, all but two escaped paralysis; several furnished unusually good indications of the incubation period; two were remarkably fine examples of the "abortive," and one of the "masked" form of the disease; moreover, three had negative spinal fluid findings and finally all five children in one family were affected.

The five children in this family, the B[2] family, were under our care; the three children of the A and C families were not seen by us during their acute illnesses, but the physicians who attended them very kindly reviewed their illnesses with us, and the parents, particularly of the A family, were extraordinarily cooperative in supplying information. Our knowledge concerning the illnesses of two children who were taken sick coincidently with the other children, one in the D, the other in the F family, was of necessity derived from indirect sources, the reason for which will be explained later, and was too meager to permit the positive conclusion that the cases were instances of poliomyelitis, though we felt very strongly that one of them at least was that disease.

At the time of the outbreak of poliomyelitis at the X House, the epidemic in the city, which had begun on July 5 and ended on Decem-

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ber 1, was at its height. Previous to the development of the first case in the X House, 85 cases of poliomyelitis had been reported, and following it there were 120 additional cases, making a total of 205 (almost all of these were of the paralytic type) in a population of about 600,000. The mortality (from the reported cases of the disease) was in the neighborhood of 33 per cent (see map).

The X House is a large, modern, five-story apartment house, containing 30 suites, situated in the northern part of the city, about three miles from its center, and bordering on one of the most fashionable residential suburbs. Though it fronts on a broad avenue, it occupies a fairly isolated position, for across the avenue, as well as on the other three sides for some little distance, there are open fields. The house is provided with all modern conveniences. The sewage system connects with that of the city. The water is also derived from the city supply, although the drinking water used by the majority of the families in the house was obtained from a spring in the immediate neighborhood. There is no public dining-room. The families living in the house obtained their groceries and meats chiefly from a store in the neighborhood, though to a considerable extent also from the stores and markets in the central parts of the city; their milk came from the various dairies of the city and their ice from a common source.

The 30 families which occupied the house consisted at the time of the outbreak of about 70 adults and 18 children, the latter varying in age from infancy to 13 years. So far as the children were concerned, it may be said that they formed a society of their own, playing with each other in and about the house, not often going elsewhere or receiving visitors from without. But it was evident that the little community of children was isolated only in a comparative sense, for plenty of lines of communication with the outside world remained open, along which the infection might have found its way to them.

Although all the children in the X House inevitably came into contact with each other, since they lived in the same building and shared a common playground, yet on account of differences or similarities in age and taste, and for various other reasons, some had little or nothing to do with the rest, while others moved in small groups or cliques. Maude S, Nancy H, Jenny J, Fritzie H and J. N. (a boy who used to come to play from the city) were older and had little to do with the others. William S, who seems to have been *persona non grata,* usually remained alone with his nurse, and Dick E was purposely kept

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from the others by his parents. Baby B and Baby A were infants in arms. The remaining 11 children were also more or less subdivided into twos and threes. Jack C and Elizabeth D were inseparable; Fritzie H and Charlie B were almost constantly together. The four older B children and the two C children, on the other hand, played little with each other, and did not go to each other's apartments, and Ned F did not have much to do with the B's but sometimes played with the C's. But all of these 11 children had this in common, that they were on especially friendly terms with the A children and frequently visited the A's apartment. In this sense it is possible to divide the children in the X House into two groups, the one group visiting the A's apartment and centering about the A's, the other group not having these relations.

The A's apartment, situated on the ground-floor of the X House, was readily accessible from the lawn. Mrs. A was exceptionally kind to the children and gave them butter-bread or wafers when they came even to the door, and her own children were especially popular, with the result that the A's apartment and back porch became a favorite rendezvous. Ned F, the great friend of Harry A, used to "spend his entire time there," the B children, except the baby, were very frequent visitors *en masse,* and often the two C children and Nancy H used to come. The A children had many toys—dolls, stuffed monkeys, Teddy bears, balls, tin horns, scissors for cutting paper dolls, etc.—and let all the visiting children use them, so that the toys passed from one to the other, and were in the A's apartment common property. The games that were played were the games of children everywhere. It should be mentioned, however, that on the lawn there was a sand-box, about 8 x 8 feet, which was used by almost all the children in the X House, even by the older children; Dick E and William S used to be taken there when the others were not present.

On September 15, 1916, the case which we regard as the first of infantile paralysis made its appearance among the children in the X House. On the evening of this day, Harry A, aged 2½ years, was taken ill. On September 11, five days previously, both he and his sister, Barbara A, 3½ years old, had what their parents regarded as a "digestive upset," accompanied by rather high fever. But both children were so much better on the following day after castor oil that they were considered well again. Harry A remained in normal health from that time until the beginning of his acute illness, five days later. He

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went to bed to all appearances perfectly well, but was found at 11 o'clock screaming with pain. He was nauseated and vomited. His temperature was 103° F.' All night he was extremely restless, slept fitfully and frequently cried out. The next day, September 16, he seemed extremely ill. His temperature was 103°. The parents now noted something never seen in any of his previous illnesses and remarked on it at the time as being very strange, that he cried whenever touched or moved, and put his hand frequently against the back of his neck. At times he seemed "out of his head." On September 17, the third day of his illness, he was seen by the family physician, who was said to have made a very casual examination and who left the impression that the illness might be a "bilious attack" or "malaria" (no blood examination was made). His temperature was then 102° F. The sensitiveness to touch continued. For the next three days Harry A remained in bed (or on a couch in the living room) except twice when taken out for a drive. On the fourth day his temperature began to fall and his condition steadily improved. During this time the parents observed that, when he was taken out of bed, he was unable to climb back into it, and that he could get on his hands and knees but had difficulty in sitting up. When Harry A was strong enough to walk, the parents became troubled at his way of doing it, and on September 23, the eighth day of his illness, made him walk before Mr. B, in order to obtain the latter's opinion. On September 24, the ninth day of his illness, they consulted their physician who, however, did not find anything wrong. After that time the little boy rapidly recovered his former strength and is now perfectly well, except that he becomes fatigued easily when walking. Apparently the possibility of poliomyelitis was not suspected, and no physical examination with that in mind was made.

Either on the day following Harry A's illness or two days later (Mrs. A does not remember which), Baby A, aged 4½ months, developed a fever of 103° F., and vomited. She is said not to have had fever previously, but to have been subject to indigestion from birth, was malnourished and vomited frequently. Her temperature did not become normal for 10 days. The baby was not seen by a physician.

Barbara A remained well during this time.

Illness next appeared in the B family, which consisted of Mr. and Mrs. B, a foreign white maid and five children. They lived on the ground floor of the X House. Mr. B used to go in the street cars each day to his laboratory in the city where, however, he was not exposed to

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poliomyelitis or any other disease. Mrs. B and the maid, who spoke no English, remained at home practically the entire time. All three were in perfect health during the month which preceded the children's illnesses. They had one guest during the summer, but he had left more than a month previously. It is an interesting fact, as possibly indicating a predisposition to poliomyelitis in the B family, that one of Mrs. B's sisters and one of her cousins are paralyzed as the result of poliomyelitis in infancy.

As already mentioned, the children of the B family were particularly intimate with the children of the A family, and frequently visited the latter. On September 16, the second day of Harry A's illness, Bobby B went to see Harry A and spent the entire morning playing with toys in the A's apartment. On the following day, September 17, Charlie B twice brought broth for Harry A and was in the A's apartment a half hour. He "caressed" Harry A but did not kiss him. On the following day or the day after, either September 18 or 19, the parents cannot remember which, Charlie B, Dorothy B and Mary B visited the A's apartment in order to see Harry A, and spent a half hour or more playing, and while there received buttered toast prepared for them by Mrs. A. It is thus seen that the contact between the B children, with the exception of the B baby, and the A children during Harry A's illness is very definite. The exception of the B baby to this contact is important, because the B baby was the only one of the B children who, within the nine days following the onset of Harry A's illness, did not contract poliomyelitis. For the two weeks previous to their illnesses the B family were not exposed, to their knowledge, to any sick person with the exception of Harry A and Baby A.

On September 21, five days after the onset of Harry A's illness, Bobby B, aged 6½ years, was taken sick. That morning he had eaten a good breakfast and had been roller-skating for two hours, when he came into the house complaining that he felt sick and his head ached. His temperature was found to be 103° F. He went to bed, seeming "a little dull," and refused dinner, but got up in the afternoon in order to see his teacher. He had a poor appetite for supper, and went to bed again immediately afterward. The next morning, September 22, he seemed so much better that his parents did not think it necessary to take his temperature and regarded him as being practically well. After a rather poor breakfast he went out of doors and remained there almost the entire day, the greater part of which he spent in roller-skating,

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coming in only for his dinner. Though he did not seem actually sick, he looked pale and did not act like himself. He went to bed without eating supper. The following day, September 23, he ate a good breakfast and went out roller-skating again, but returned at 11.30 looking very ill. It seemed to his parents that a sudden change had taken place; his temperature was 103° F., and he again complained of severe headache. He was put to bed at once and soon became so drowsy that it was necessary "to shout" to get an answer. He now began to complain of pain in the back of his neck and in the front of his head, and at seven in the evening he vomited. The following day, September 24, he seemed slightly better and no longer complained of headache, and played with paper dolls. His temperature was 102.5° F. When seen late that afternoon by one of us, he was in bed, rational, and did not complain of pain, but looked very sick and exhibited the restless behavior of children with a high fever, though his temperature was only 102.5° F. His face underwent frequent choreiform-like contractions. Some nasal obstruction was present, but unaccompanied by discharge. The knee and ankle jerks were exaggerated. No clonus was present. On attempting to obtain the Kernig sign, marked pain was elicited. There was well-marked general hyperæsthesia; otherwise, the physical examination was negative. That evening he became much worse, complaining of pain everywhere, and evidently paralysis had begun to manifest itself, for he could not stand. The following morning, September 25, he was again seen by one of us. His legs were almost completely paralyzed, though some slight motion of the left great toe was still present. Knee and ankle jerks were now absent. The diaphragm seemed to be completely paralyzed and thoracic respiration was feeble. Each inspiratory movement was accompanied by marked dilatation of the nostrils and gasping movements of the mouth. Slight internal strabismus had appeared, and the left pupil was smaller than the right. About 1.30 p. m. there was a general convulsion. From this time on respiration was kept up by means of a "pulmotor." He was transferred to the poliomyelitis hospital. On arrival, spinal fluid was obtained, which showed 250 cells and a positive reaction for globulin. He was given 10 c. c. of immune serum intraspinally. He died at 1.30 the following morning.

At necropsy, the typical lesions of acute poliomyelitis were found. There was a general lymphatic hyperplasia, most marked in the solitary nodules of the large and small intestines, Peyer's patches, and the

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mesenteric lymph nodes. The brain was soft and congested. The pons, medulla and spinal cord were swollen and œdematous. There was a sterile fibrino-purulent exudate over the surface of the spinal cord (injection of immune serum). Microscopical examination showed hyperæmia, extensive perivascular and diffuse infiltration of cells, mostly mononuclear cells, nerve cell degeneration and neurophagocytosis in the tegmenta of the pons and the medulla and especially in the anterior horns of the entire cord.

On September 23, two days after Bobby B was first taken sick, at about 10 o'clock in the evening it was noticed that Mary B, aged 2½ years, did not seem well. The next morning, September 24, her temperature, taken for the first time, proved to be 103° F. Since her parents found it difficult to keep her in bed, they dressed her and allowed her to sit or wander about the house throughout the day. When seen in the late afternoon of September 24, by one of us, her temperature was 102.5° F. She looked pale, but did not act especially sick and did not complain, and gave no indication of headache. No examination was then made except to determine that both knee jerks were present but not active, that no paralysis existed, and that her throat was clear. Her gait was normal. The next day, September 25, she seemed somewhat better, but was removed to the poliomyelitis hospital. On her arrival there she was very drowsy and irritable when disturbed; her temperature, however, was 99°. Physical examination revealed nothing. A spinal puncture was done; the fluid obtained contained a trace of globulin, but only five cells per cubic millimeter. (The physician who made the puncture is certain that there was no admixture of blood.)

Three days after the beginning of Bobby B's illness, and on the day following the illness of Mary B, namely, September 24, Charlie B, aged 9½ years, was suddenly taken ill. Charlie had eaten a fairly large breakfast that morning and had been out of doors playing, but returned to the house about noon, complaining of severe headache. His temperature was 103° F., and he was immediately put to bed. When seen late that afternoon by one of us his temperature was still 103°; his face was flushed. He lay in bed, appearing in great distress, with his hand pressed against his forehead. He continually tossed about and his face twitched. On examination it was noted that the knee jerks were hyperactive; well-marked hyperæsthesia was present, and flexion of the extended leg in the attempt to obtain Kernig's sign seemed to produce

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a great deal of pain. The neck was not stiff, and in other respects the physical examination was entirely negative. On the morning of the next day, September 25, the temperature was 102° F., but his condition was greatly improved. He was found sitting up in bed, cutting out paper dolls, and said his headache had entirely disappeared. A leucocyte count taken at this time showed 19,000 white blood cells. The physical examination was entirely negative, except that the knee jerks were still over-active. That afternoon, at about 2 o'clock, he was transferred to a poliomyelitis hospital with his brother and two sisters. On arrival his temperature was 99.2°, and lumbar puncture showed five cells and a negative reaction for globulin. Eight cubic centimeters of immune serum were given, however, intraspinally. The urine contained albumin. The boy quickly recovered his normal condition. A lumbar puncture repeated on October 11, 17 days after the onset of his illness, showed a clear fluid, which gave a negative globulin and contained only two cells to the cubic millimeter.

At half past five in the afternoon of September 24, Dorothy B came into the house complaining of headache. She had been out of doors almost the entire day, had eaten her usual dinner, and seemed in her customary health. Her bowels had moved normally. Her temperature was immediately taken and found to be 104° F. She was put to bed. Her face was flushed. She seemed to her father very ill. She held her head and complained of headache exactly as her brother Charlie B had done. On the following morning, September 25, she was seen by one of us. A physical examination revealed nothing excepting overactive knee jerks. She was found sitting up in bed and stated that her headache was gone. Her temperature was then 102.5° F. At 2 o'clock in the afternoon she also was taken to the poliomyelitis hospital. On admission her temperature was 101.6°; pulse 140. Physical examination was negative. The spinal fluid showed three cells per cubic millimeter, and a negative test for globulin. She was given, however, 10 c. c. of immune serum intraspinally. The following day her temperature was normal. On October 11, 17 days after the onset of her illness, spinal fluid was again obtained; it contained nine cells per cubic millimeter and the test for globulin was negative.

On September 24 the illness appeared also in the C family. The C family was composed of Mr. and Mrs. C, Mrs. C's mother, and two children, Jack and Billy. At this time they had no servant. Mr. C, a business man, went to his work daily, using the street cars. Mrs. C and her

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mother had been out of the house very little during the two weeks which preceded Jack C's illness. Neither Mr. C, Mrs. C, nor Mrs. C's mother had been exposed to any illness, so far as they were aware, and the children had not been in contact with any sick person excepting Harry A.

Jack C was 6 years old. About a week before the beginning of his acute illness he had a digestive upset (a frequent occurrence). This kept him indoors until September 21. On that day, his physician allowed him to go out. In the morning he and his brother, Billy C, were taken for a half hour's drive by Mrs. A in the governess pony-cart, together with Elizabeth D and Barbara A and Harry A. It was the fifth day of Harry A's illness, and he was still so weak that he had to be lifted in and out of the pony-cart. Mrs. A, who drove, recalls that Elizabeth D and Barbara A, who were seated in the pony-cart next to Harry A, quarreled so much that she removed Elizabeth D, putting Jack C in her place, so that Jack C and Harry A sat next each other for the greater part of the drive. Mrs. A says that the only reason she remembers the incident is that, when Jack C was placed next to Harry A, she noticed that both children looked pale. Mrs. A also says that the pony-cart was so small and on this drive so crowded that all the children sat with their heads close together. Jack C was not exposed to any sick B person during the two weeks preceding his acute illness, except to Harry A on this occasion.

At 2 o'clock on the morning of September 24, the day on which Charlie B and Dorothy B were taken sick, Jack C awoke his parents complaining of headache and shortly afterwards vomited. His parents took it for granted that Jack C was suffering from another of his digestive upsets, but by the next morning, September 25, his condition had become so serious that they called in their family physician. Jack's temperature was then 102.5° F., the headache had become more intense and vomiting had recurred a number of times. When the physician arrived, he found well-marked rigidity of the neck, increased reflexes, a positive Kernig sign and an extreme degree of hyperæsthesia. The boy was extremely drowsy; occasionally he cried out in his sleep and twitched convulsively; at times he was delirious. On September 27, the third day of his illness, a lumbar puncture was performed. The spinal fluid was sterile, but contained 173 cells to the cubic millimeter, a preponderance of which were polymorphonunclear leucocytes; the globulin test was faintly positive. At this time his temperature was

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102.3° F. In the course of the next three days the temperature fell to normal and all symptoms disappeared. No paralysis developed. For the five weeks which followed he was kept in bed and the family have no idea whether any muscular weakness was present. He is now, January 1, 1917, entirely well.

The next child to be taken sick was Ned F, 3 years old. The F family was composed of Mr. and Mrs. F, their only son, Ned, and two servants. For some time Mrs. F and Ned had been at a summer resort which was considered free from poliomyelitis. They had returned to the X House only seven days before Ned became ill. None of the adults in the family had been exposed to any sick person so far as is known, and were themselves well previous to Ned's illness. Ned F, as will be remembered, was a special friend of Harry A, and during Harry A's illness Ned F was repeatedly in the A's apartment. Mrs. F took Ned F and Harry A for an hour's drive in her automobile on September 20, the fourth day of Harry A's illness. Harry A was so sick at the time that he was carried to and from the automobile. We could not learn that Ned F was exposed to any other sick child than Harry A.

We do not know the exact details of Ned F's illness. Indeed at first it was denied altogether, and later only the fact was admitted. From other sources we have learned, however, that on September 25, the day on which the B children were removed to the hospital, Ned F was taken sick and vomited. At noon of that day Mrs. F, learning that the B children had infantile paralysis, in great excitement wrapped Ned in a blanket and left the city. She is reported to have said that Ned looked so sick that she could not understand how she succeeded in passing the officials at the railroad station, that he vomited several times that day and night and felt hot, that she was terrified, and that he did not seem well again for 10 days. We also learned that Mrs. F said she felt perfectly sure Ned had the disease. At any rate, he did not develop any paralysis and is now well.

On the day on which the B children were removed to the hospital and Ned F was taken sick, Elizabeth D, aged 5, the only daughter of Mr. D, an employee of the X House, became ill. The D family lived in the basement of the X House, and consisted of Elizabeth D, her father and an aunt. We could discover little in regard to her or her family during the two weeks which preceded her illness. We cannot find that she entered the A's apartment or came in contact with Harry A during his illness, except on one occasion, namely, during the half hour's drive

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in the pony-cart on September 21, the fifth day of Harry A's illness. Her boon companion was Jack C, and, if Elizabeth D had poliomyelitis, we should expect to find that her exposure occurred at the same time as that of Jack C. (See page 395.)

We have very little information in regard to Elizabeth D's illness. Her father denied to us that she was sick at all, but he told at least three of the residents of the X House that she was "very sick" on the night of September 26, and that he was "scared for fear she had infantile paralysis"; in fact, a resident of the X House informed us that he knew at the time that Elizabeth D was ill because he was kept awake by her screaming. The doctor who visited Elizabeth D informs us that she had an earache. He did not examine her ear-drum, and her ear never discharged. Whatever the nature of her illness, it is certain that she was suddenly taken sick coincidently with the others.

The next child to become ill was Billy C, aged 4. It will be remembered that Billy C was present, as well as his brother, Jack C, on the drive in the pony-cart with Harry A. On September 28, four days after Jack C's illness began, Billy C was suddenly taken sick. The evening preceding, the family doctor saw him and testifies that he was in normal health. At 1 o'clock in the morning he awakened his parents complaining that he could not sleep. At 8 o'clock he vomited. His temperature was then between 104° and 105° F. He had no headache, but complained of pain in the back of his neck. When seen by the physician, the neck was rigid, the Kernig sign positive; the tendon reflexes were exaggerated; marked general hyperæsthesia was present. At times he was delirious. In fact, his illness was more severe than that of his brother. At the end of six days his symptoms had entirely disappeared and no paralysis occurred. He, too, was kept in bed for five weeks, at the end of which time he seemed to have recovered entirely.

Baby B, the only one of the B children who had thus far escaped infection, was a healthy baby, 4½ months old, but weighing only 9 pounds. Her mother used to keep her out of doors on the lawn in a basket for a large part of each day, when the weather was pleasant, but had not done so during the nine days which preceded her illness, because of the illness of Bobby B and the other children. Baby B's brothers and sisters came into the closest contact with her and, of the four, Bobby was the most devoted to her, often kissing and caressing her. Dorothy B frequently carried the baby about in her arms, and in

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the early morning it was the parents' custom to take the baby into their own bed, where the other children gathered to play with her. The parents vividly recall that on September 22, during the intermission which ensued between the acute symptoms of the onset of Bobby B's illness and those which preceded his death, he repeatedly kissed and fondled the baby.

Immediately preceding her acute illness, Baby B was perfectly well, except for a slight cold, and did not come in contact with any sick person except her brothers and sisters.

At 6 o'clock in the evening of October 1, the baby was exhibited to a guest, a physician, and gave every sign of being in perfect health. At 10 o'clock Mrs. B observed that the baby's skin felt hot, but did not take her temperature for lack of a thermometer. The baby took the 10 o'clock feeding well, but afterwards seemed very sick, sleeping hardly at all and frequently crying out as if in pain. The parents, alarmed, remained awake the entire night. The following morning, October 2, the baby's temperature was found to be 102.5° F. She was exceedingly restless and very hyperæsthetic. Her bowels moved normally and there was no vomiting. Late in the afternoon of October 2 the baby was seen by one of us. She looked very ill, frequently crying out, and screamed when touched. The fontanelle was full, the pulsations were particularly pronounced. Retraction of the neck was apparent, and when the head was flexed upon the chest she screamed, though she did not resist the flexion. The knee-jerks were much exaggerated and the ankle-jerks easily obtained, but there was no clonus and no Kernig sign. No paralysis was present. A lumbar puncture was twice done and bloody fluid obtained, under apparently normal pressure. That evening the temperature rose to 103.6° F. By the following morning, October 3, the third day of the disease, paralysis had appeared, with involvement of the left deltoid, pectoralis major and triceps muscles. On this day the baby was removed to the poliomyelitis hospital. On arrival a lumbar puncture was performed; the clear fluid obtained contained 270 cells to the cubic millimeter and remained sterile. During the course of the day, weakness developed in the flexor muscles of the left leg. The temperature continued elevated for four days and then fell to normal. The baby still (January 1, 1917) has paralysis of muscles of the left arm.

Thus, of the 11 children who formed the group which came into especially intimate contact with the A family, all but two developed

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TABLE NO. 1 INDICATING AGE AND FAMILY GROUPING OF CHILDREN AND EXPOSURE TO AND INCIDENCE OF POLIOMYELITIS AMONG THEM.

Children of	Age.	Exposure to Harry A or his immediate environment.	Poliomyelitis.	Unexplained illness occurring coincidently with the cases of polio.	No illness.	Outcome. Form of disease.
A Family.						
Barbara..	3½ yrs.	+ (See foot-note.)[4]	.....	.....	+	
Harry....	2½ yrs.	.....	+	.....	.....	Recovery. Non-paralytic.
Baby.....	4½ mos.	+	.....	+ (see page 390)	.....	Recovery.
B Family.						
Charlie..	9½ yrs.	+	+	.....	.....	Recovery. Abortive.
Dorothy..	8½ yrs.	+	+	.....	.....	Recovery. Abortive.
Bobbie...	6½ yrs.	+	+	.....	.....	Death. Ascending paralysis.
Mary	2½ yrs.	+	+	.....	.....	Recovery. "Masked" form.
Baby.....	4½ mos.	0 but (exposure to brothers and sisters) see page 397	+	.....	.....	Recovery with paralysis.
C Family.						
Jack.....	6 yrs.	+	+	.....	.....	Recovery. Non-paralytic form. Spinal fluid.
Billy.....	4 yrs.	+ See page 397 (and to Jack C)	+	.....	.....	Recovery. Non-paralytic.
D Family.						
Elizabeth.	5 yrs.	+	.....	+ (see page 396)	.....	Recovery.
E Family.						
Dick.....	2 yrs.	0	.....	.....	+	
F Family.						
Ned.	3 yrs.	+	.....	+ (see page 396)	.....	Recovery.
S Family.						
Maude...	13 yrs.	0	.....	.....	+	
William..	5 yrs.	0	.....	.....	+	
J Family.						
Jenny....	12 yrs.	0	.....	.....	+	
N Family.						
J N*.....	.....	0	.....	.....	+	
H Family.						
Nancy ...	8 yrs.	0	.....	.....	+	
Fritzie...	12 yrs.	0	.....	.....	+	

* J. N. does not strictly belong to the group of children in the X house. See page 388

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some kind of an illness within a week of each other, and within the 13 days which followed the onset of Harry A's illness. The two who escaped were Barbara A, Harry A's sister, and Fritzie H. Barbara A was, of course, more exposed to infection, provided it centered about her brother or in the A's apartment, than any other child in the X House, and ought under those circumstances to have contracted the disease before any of the others.[4] We cannot find that Fritzie H, on the other hand, entered the A's apartment at all or came in contact with Harry A during his illness and, if exposure in the A's apartment or to Harry was essential for infection, ought to have escaped it. She was exposed, however, to Bobby B on September 22, the day marking the intermission period of his illness, for on that day she was taken for a drive with him and Barbara A in the A's pony-cart; but she remained well (Table 1).

Experiments.

The following experiments were planned with a view of proving that certain of the cases of illness among the children in the X House, not accompanied by paralysis, were poliomyelitis, and in the hope that by the method employed we might be able to trace the outbreak back to its starting point:

Experiment I (a), October 13, 1916.—*Ringer's solution washings of the nose, mouth, pharynx and intestines of Charlie B, obtained when in perfect health 19 days after the onset of his illness; the filtrate injected into a monkey.*

The washings of nose, throat and mouth were made by passing the Ringer's solution through these passages several times, until it was rich in mucus. The intestinal washings were obtained in a similar manner, after the fecal matter had been removed by means of a normal saline enema. Both sets of washings were mixed together, shaken and passed through a Berkefeld filter, which would not allow the passage of the *B. violaceus*. Fifty cubic centimeters of filtrate were obtained, 2 c. c. were injected into the left lateral ventricle and 10 c. c. into the peritoneal cavity of Macacus rhesus, No. 1, a small monkey which had been in the laboratory about four years. The monkey appeared healthy. The injections were made under ether anæsthesia.

This monkey recovered at once and remained well for 48 hours. He then showed weakness in his right hind leg, later in his left hind leg and a prolapse of the rectum developed. He dragged his hind parts. On the fourth day his front legs became weak and his respirations rapid. He was unable to lift himself from the floor. He was not, however, completely paralyzed in any of his extremities. On the fifth day his respirations

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became slow and labored and he died. At autopsy, no lesions of the organs were found excepting hyperplasia of the lymphatic nodules of the spleen, stomach, intestines, lungs and lymph glands. The brain appeared normal. The cord was hyperæmic but not œdematous. There were a few hemorrhages into the cord and medulla, but no cellular infiltration except in one small area in the floor of the fourth ventricle. A small part of the floor was infiltrated with round cells and a few of the neighboring veins showed perivascular infiltration. A number of the sensory ganglia were examined, but no lesions were made out. A piece of the cord was taken aseptically and placed in 50 per cent glycerine.

EXPERIMENT I (b).—December 2, 1916. *Injection of an emulsion in physiological salt solution of the glycerinated cord of Monkey No. 1 into Monkey No. 2, a healthy Macacus rhesus.*

One cubic centimeter was placed into the left lateral ventricle and 4 c. c. into the peritoneal cavity of this monkey.

EXPERIMENT I (c).—December 12, 1916. *A thick emulsion in physiological salt solution of another part of the glycerinated cord of Monkey No. 1, injected into Monkey No. 5.*

One cubic centimeter of the emulsion was placed in the left lateral ventricle and 1 c. c. into the peritoneal cavity.

Both of these monkeys have remained well up to the time of writing, January 22, 1917.

EXPERIMENT I (d).—October 29, 1916. *Nasal, pharyngeal and intestinal washings again taken from Charlie B and from his sister, Dorothy B, 35 days after the onset of their illnesses and injected into monkeys.*

Nasal and pharyngeal washings of the two children were mixed together, filtered, and 2 c. c. of the filtrate were introduced into the left lateral ventricle and 10 c. c. into the peritoneal cavity of a large, healthy monkey, No. 4.

The intestinal washings of the two children were kept separate, shaken and filtered and injected in the same manner, each into one of a pair of young healthy Macacus rhesus, Monkeys Nos. 5 and 6. These monkeys were well at the end of six weeks.

EXPERIMENT II.—October 21, 1916. *Washings of the naso-pharynx, mouth and colon of Harry A obtained in manner described in Experiment I, 36 days after onset of his illness, injected into large Macacus rhesus, No. 3.*

Two cubic centimeters were injected into the left lateral ventricle, 40 c. c. into the peritoneal cavity. The filtrate contained very little mucus. The monkey was reported to have remained well.

DISCUSSION.

Flexner and Lewis found that the filtrate of an emulsion of the nasal mucous membrane of a monkey having poliomyelitis produced the disease when inoculated into a healthy monkey. Following this experiment a number of investigators, Landsteiner and Leviditi, Leiner and

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V. Wiesner, Römer, Strauss, Rosenau, Sheppard and Amoss and Gins attempted to transmit the disease to monkeys by means of a Berkefeld or Chamberland filtrate of material obtained from the nose, pharynx or mouth of patients ill with the disease.[4] All the experiments were negative.

In February, 1911, Osgood and Lucas[5] reported successful transmission of the disease to healthy monkeys by means of a Berkefeld filtrate of an emulsion of the nasal mucous membrane obtained from monkeys dying without other demonstrable infection six weeks and five and one-half months after the acute stage of the disease.

By far the largest number of experiments of this kind were performed by Kling, Pettersson and Wernstedt, 1912.[7] They attempted to transmit the disease to monkeys by means of a filtrate of the secretion of the nose, mouth, pharynx, trachea and intestines of persons dead with the disease, acutely ill with it, having recently recovered and having recently been exposed to it, and healthy persons who apparently had had no contact with the disease. These investigators report a large number of positive results. The technic that they used differed in one important particular from that of their predecessors; instead of a Berkefeld, Chamberland, or other filter, they used a Heim, which is more permeable.

In 1913, Flexner, Clark and Frazier[8] washed with normal saline solution the nose, mouth and pharynx of healthy parents of a child sick with the disease. It was shaken and passed through a Berkefeld filter. One and a half cubic centimeters were injected into the sciatic nerve and 140 c. c. into the peritoneal cavity of monkeys. The animals developed typical symptoms, and the authors state that the cords showed typical and characteristic lesions of the disease.

It is seen that the disease has been successfully transmitted from infected human beings to monkeys. But the majority of investigators who have attempted thus to transmit the disease have been unsuccessful. Although Kling, Pettersson and Wernstedt report a large number of positive results, and a high percentage of their inoculated monkeys showed symptoms certainly strongly suggestive of poliomyelitis, the positive interpretations which they put on the results of many of their experiments are open to criticism, in that they accepted purely degenerative changes in the nervous system as a final criterion for the diagnosis of this disease. In fact, the large number of positive results reported by Kling, Pettersson and Wernstedt are difficult to reconcile

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with the observations of Flexner and Lewis[9] and other investigators, according to which monkeys frequently fail to become infected, even when an emulsion of the spinal cord of another monkey dead of the disease is used; and further, it is known that human strains are often less virulent to monkeys than strains that have undergone preliminary passage through monkeys which are more susceptible to the disease.

Negative results following the inoculation of monkeys with secretions which are supposed to contain the virus of poliomyelitis mean nothing.

In our experiments the material was obtained three and six weeks after the acute stage of the disease, and after the children had been well for some time. No attempt was made to concentrate the material, and the material injected was small in amount.

Discussion of Diagnosis.

The clinical diagnosis of poliomyelitis is ordinarily made when a flaccid paralysis suddenly develops without apparent cause in the course of a short, otherwise unexplained, febrile illness, usually marked by symptoms of involvement of the central nervous system; it receives corroboration if certain fairly characteristic changes also occur in the spinal fluid. The paralysis may be so extraordinarily distinctive in the suddenness of its development and selection of muscle groups as alone to establish the diagnosis, but the constitutional manifestations of the disease are never in themselves sufficient to distinguish it from certain other infections. Under unusual conditions, however, the circumstantial evidence favoring poliomyelitis may be so overwhelming as to justify that diagnosis when the constitutional symptoms only are present, that is, when poliomyelitis is in the community in epidemic form and side by side with the case in question, which cannot be explained otherwise, and when in the same family or house, or among playmates manifest cases of the disease develop having identical onset and symptoms.

Such were the unusual conditions that obtained in the outbreak at the X House; eight children living in the same house with definite association proved; all taken abruptly sick, without apparent cause, within 15 days of each other, six of them within eight days of each other; seven of them obviously having the same disease, as judged by the mode of onset, symptoms and physical signs, and three of the seven

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proved to have poliomyelitis by the development of paralysis or changes in the spinal fluid."

The diagnosis of poliomyelitis in the case of Mary B, who did not show all of the symptoms of the others, depended on circumstantial evidence alone. It will be remembered that her illness was characterized only by fever, pallor and malaise. The onset may have been sudden, headache may have been present, but neither was apparent (she was only 2½ years old). The coincidence of her illness, otherwise unexplained, with the illnesses of her four brothers and sisters, leaves no alternative but to regard the illness as poliomyelitis also.

When we come to the illnesses of Ned F and Elizabeth D, it must be said that the data in our possession are insufficient to permit any definite conclusion. But we feel it is not without significance that these two children were abruptly taken sick, five to seven days after exposure to Harry A (Ned F at least, without apparent cause), and coincidently with the six other children. Elizabeth D's "earache" might have been the violent headache which was so marked a symptom in the other cases. We can form no idea whether the illness of Baby A was poliomyelitis or not.

Mode of Conveyance of Infection.

Although now it is very generally believed that poliomyelitis is an infectious disease, there exists considerable difference of opinion in regard to its mode of conveyance from one person to another. The theory which has received most support from clinical experience and experimental investigations on monkeys, is that the infecting material is contained in the discharges of the carrier of the disease and conveyed to the non-infected by direct contact or through the medium of contaminated objects, such as toys, food, clothing, etc. (Wickman, Kling, Pettersson and Wernstedt, Flexner and others), or possibly through the agency of filth-carrying insects, such as the fly. But others have ascribed the conveyance of infection to blood-sucking insects. The stable fly (Rosenau and Brues [11]) the bed-bug (Howard and Clarke [12]), the rat flea (Richardson [13]), and other insects have been thought to be the agents of conveyance.

We investigated the question of insects and insect-carrying animals at the X House, but failed to find any evidence that insects could have been the source of the infection. The X House and its environs were probably as nearly free from them as any house or locality in the city. There were no fleas, and we cannot find that the stable fly was common

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in that locality. But aside from these considerations, the theory of the transmission of poliomyelitis by biting insects does not explain the facts of the outbreak at the X House; for one group of children was affected and the other spared; moreover, the children in the affected group developed the disease suddenly, six children (possibly eight) almost together, and the outbreak was begun and ended in two weeks.

We also investigated the sanitary conditions at the X House (garbage disposal, etc.), and the food and water supplies of the different families without bringing to light any facts indicating the introduction of the infection through those channels. So far as we are aware, there was no single kind of food or a food derived from a particular source, except perhaps sweetmeats, which was common to the affected families and not to any of the others. The case of the B baby, however, renders the food transmission theory untenable, in one instance at least, for the baby received different food from that of all the other affected children,[24] and yet contracted the disease.

The theory of infection through human contact, on the other hand, furnishes the likely interpretation of the facts.

If the analysis of the outbreak of poliomyelitis in the X House indicates one thing more than another, it is that the primary spreading point of the infection was in the A apartment, or connected in some way with the A family, in all probability centering about Harry A. The crux of the problem seemed to be, therefore, to discover how the disease found its way into the A family.

Mr. A was in the habit of going to his office in the city each day by the street cars, but was not aware of contact with any case of poliomyelitis or any sick person. Mrs. A left the X House very little during the period which preceded Harry A's illness and met, to her knowledge, no one who had poliomyelitis or any other disease. The colored maid,[25] 19 years old, the laundress also colored, who did her work outside the A's apartment, P. V., the boy who drove the pony-cart, and P. V.'s friend, were each visited at their homes without bringing to light any association with any case of poliomyelitis there or elsewhere.

The only other person from without, who came in contact with the A children during the critical period which preceded Harry A's illness, was Mrs. A's father, Mr. W, an elderly man, a resident of New York, and accustomed to travel about extensively. On September 6, nine days before Harry A was taken ill, he had come directly from New York, where poliomyelitis was then at its height, to visit his

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daughter; remained for a day and night in the A's apartment, and while there came in close contact with the children; in Mrs. A's words, "the children climbed all over him." But except for the fact that he came from an infected locality, and that the date of his visit preceded the date of his grandson's illness by a comparatively short interval, there seemed to be little reason for supposing him to be the carrier of the disease. We desired to learn whether he had come into contact with poliomyelitis, or had been ill himself prior to his visit to his grandchildren, but were unable to obtain this information. We also sought to test him for poliomyelitis by the inoculation of monkeys with filtrates of his secretions, but without success. We were, therefore unable to discover the origin of Harry A's illness and of the outbreak in the X House.

We think, however, we have obtained evidence that the disease was transmitted from person to person after it had found entrance to the X House. At least, we have been able to show that all those children developing the disease after Harry A were exposed to Harry A with the exception of Baby B, and became ill with the disease from three to eight days after the exposure; that Baby B, on the other hand, was in her turn exposed to Bobby B and the other B children, and developed the disease less than nine days afterwards; that all the children exposed to Harry A during his illness developed the disease with the exception of Barbara A, Harry A's sister, and perhaps also Ned F and Elizabeth D,* and that none of the children not exposed to Harry A (with the exception of Baby B, just mentioned), on the other hand, developed poliomyelitis.

A consideration of the incubation period of all the children calculated on the supposition that the outbreak took origin from Harry A, or his environment, also lends support to this view (see Table 2). The shortest incubation period was that of Jack C (exposed to Harry A on September 21, during the drive in the pony-cart); it was three days long. The incubation period of his brother, Billy C, was four days, if he acquired the disease from Jack C, seven days if from Harry A, during the drive in the pony-cart just referred to. His exposure to his brother, Jack C, was particularly close, because the family, not appre-

* Ned F and Elizabeth D, it will be remembered, were both taken sick on September 26, four to seven days after their exposure to Harry, but the data in regard to their illnesses were not sufficient to form a definite judgment.

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TABLE No. 2 GIVING EXPOSURE TO AND ONSET OF POLIOMYELITIS IN THE CHILDREN IN THE X HOUSE.

Sept. 15...	Harry A develops poliomyelitis.								
	Bobby B	Mary B	Jack C	Charlie B	Dorothy B	Ned F*	Elizabeth D*	Billie C	Baby B
16...	Exp. A	....	....	....	....	Exp. A?	....	....	....
17...	Exp. A	....	....	Exp. A	....	Exp. A?	....	....	....
18...	Exp. A	Exp. A	....	Exp. A	Exp. A	Exp. A?	....	....	....
19...	Exp. A	Exp. A	....	Exp. A	Exp. A	Exp. A?	....	....	....
20...	Exp. A	Exp. A	....	Exp. A	Exp. A	Exp. A	....	....	....
21...	Onset	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A?	Exp. A	Exp. A	Exp. B
22...	....	....	....	....	....	....	....	....	Exp. B
23...	....	Onset	....	....	....	....	....	....	Exp. B
24...	....	....	Onset	Onset	Onset	....	....	Exp. C	Exp. B
25...	....	....	....	....	....	Onset	Onset	Exp. C	Exp. B
26...	....	....	....	....	....	....	....	....	....
27...	....	....	....	....	....	....	....	....	....
28...	....	....	....	....	....	....	....	Onset	....
29...	....	....	....	....	....	....	....	....	....
30...	....	....	....	....	....	....	....	....	....
Oct. 1...	....	....	....	....	....	....	....	....	Onset

Exp. A = Exposure to Harry A.
Exp. B = Exposure to the B children.
Exp. C = Exposure to Jack C.
* = A definite diagnosis of the illness not made.

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ciating the nature of Jack C's illness for two days, made no attempt to keep the two boys apart during that time. Bobby B's incubation period was probably five days, though it may have been less. He came in contact with Harry A two or three days before his brother and sisters, and developed the disease two or three days before they did. This rather remarkable correspondence between the time of exposure and of onset made it seem likely that his infection dated from the first day of his exposure to Harry A, which would make the incubation period five days. The incubation periods of Mary B, Dorothy B and Charlie B calculated from their exposure to Harry A, lie between two and seven days, and seemed fairly definite. (Of course, it was possible that Mary, Dorothy and Charlie B contracted the disease from their brother, Bobby B, but a consideration of all the facts makes that source of infection less probable.) Baby B's incubation period, calculated from her exposure to her brothers and sister, may be six days. The contact between her and Bobby B, in the intermission period of the latter's illness, was so intimate (he was repeatedly seen to kiss her) that we have felt inclined to date her infection from that time, which would make the incubation period seven or eight days; but she may have acquired the infection from Bobby B, or the other children later, or from infected material left by them in the apartment (see appendix). In general, it may be said that the estimated incubation periods of the children compare with each other in quite a remarkable way, and that the curve formed by plotting out the dates of known exposure parallels the curve representing the dates of onset as nearly as would obtain if the outbreak had been measles or scarlet fever instead of poliomyelitis. The average duration of the estimated incubation periods is four to five days.[20]

Unusual Features of Outbreak.

We wish now to point out several features of the outbreak of poliomyelitis at the X House which are of unusual interest. The first is the remarkable coincidence of the appearance of the disease in all five children of one family. Pasteur [21] reported seven cases in one family, three of which were of the paralytic form. The largest number of reported cases of poliomyelitis in any one family during the great New York epidemic of the past summer was four.[15] Reece [19] reported the development of nine cases of poliomyelitis in an ordinary dwelling house, but involving more than one family.

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Another interesting feature of the outbreak of poliomyelitis at the X House was the variety of forms in which the disease manifested itself. The case of Bobby B was the fatal form of *ascending paralysis.* The cases of Harry A, Jack C and Billy C were typical examples of the *non-paralytic* form of the disease. The acute symptoms lasted the full period, five or six days, and their severity was such as to have warranted the assumption that paralysis would follow. The illness of Charlie B and Dorothy B, characterized by violent onset with symptoms suggestive of meningitis, but subsiding within 48 hours, are excellent examples of the *abortive* form of the disease. Mary B, on the other hand, represents "masked" poliomyelitis (the "larvierte" form of Müller). This case would never have been recognized except for its association with the others. It is these last two forms which Wickman and others regarded as a special menace to the community.

Another feature of considerable interest is the absence of changes in the spinal fluid in three of the cases, Mary B,[32] Charlie B and Dorothy B. We cannot find, in the recent literature, a description of any case of poliomyelitis in which the spinal fluid was found to be normal. As a matter of fact, little is known about the spinal fluid in the abortive and "masked" forms of the disease, for the reason that a spinal puncture is almost never made in these cases.

The occurrence of so large a proportion of non-paralytic forms of poliomyelitis among the affected children in the X House is interesting and is probably not so unusual as might first appear, because the milder forms ordinarily escape recognition (Wickman,[31] Leegaard,[33] Müller,[34] Kling, Pettersson and Wernstedt[35] and others). A careful investigation by Wickman of separate outbreaks of poliomyelitis in small isolated Swedish villages for such cases revealed that 35 per cent, 46 per cent and 56 per cent, respectively, of the total number of cases were non-paralytic. Wickman estimated that 50 per cent of the cases in epidemics of poliomyelitis were non-paralytic. Leegaard expressed a similar opinion. Edward Müller, who investigated the epidemic of poliomyelitis in Hessen-Nassau, Germany, in 1909, came to the conclusion that the abortive forms far exceeded the paralytic and were especially common among adults. Reece, who studied the "Stokes River epidemic" of poliomyelitis in England, reported 33 abortive cases of poliomyelitis out of a total of 36. Kling, Pettersson and Wernstedt state: "According to our experience the virus carriers and the abortive cases in a family may be four to five times as numerous

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as the cases showing typical symptoms." And finally, even the statistics of the New York epidemic, which has just concluded, show that the non-paralytic cases have been more numerous than those showing paralysis. In the X House, the proportion of non-paralytic cases is over 60 per cent.

Finally, how can we reconcile the facts that in the outbreak at the X House the disease occurred in so severe a form in one case and so mild a form in most of the others? And what is the significance when the incidence of the disease, in a given community, is high and the proportion of mild forms relatively great? We can only theorize in answer to these questions. We wish to point out, however, that the severity of the disease in the case of Bobby B may be explained on the ground of excessive physical exertion (it will be remembered that he roller-skated throughout the second and the morning of the third day of his illness). Wickman writes in this connection: "Exercise during the initial stage seems unfavorably to influence the further course of the disease and seems to tend to induce a relapse."

The significance of a high incidence of the disease in a community or a house must be that the infecting material is widespread and easily accessible, so that a large number of persons become infected. The significance of the large proportion of mild cases, as observed in all the carefully studied epidemics, we would regard as indicating that the larger number of persons are under ordinary conditions little susceptible to the disease. If it is true that relatively few are naturally susceptible it should be found that when the incidence of poliomyelitis is high, the relative number of non-paralytic forms is high; that is, the two vary directly with each other, and the greater the one, the greater also the other.

In conclusion, we wish to point out from our experience that a focus of infection in a city or in a house occupied by numerous families or in an institution cannot, from the nature of things, be ideal for the study of the epidemiology of poliomyelitis. The contacts are so numerous that the investigator, attempting to trace the path of the infection, becomes lost in a maze of difficulties. The ideal conditions for such a study are still to be looked for, as Wickman originally pointed out, in a thinly settled community in which contacts occur, but every one of these contacts is an event.

We wish to express our appreciation to Dr. Simon Flexner of the Rockefeller Institute for Medical Research, New York City, and to

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Dr. G. W. McCoy, of the United States Public Health Service, Washington, D. C., for supplying monkeys for some of our experiments.

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1. Wickman, Ivan: Acute Poliomyelitis (Heine-Medin's Disease). Translated by J. Wm. J. A. M. Maloney, Monograph, Nervous and Mental Disease Series, No. 16, New York, 1913.
2. In the presentation the families will be designated as A, B, C, D, etc., the children by fictitious first names.
3. All temperatures are oral, excepting in the case of Baby B, in which they are rectal.
4. It will be remembered that Barbara A was ill on September 11, with a temperature of 104°. It is possible that she had poliomyelitis at that time, but scarcely probable, because her illness was in no way typical and could be explained on dietetic grounds.
5. See Kling, Pettersson and Wernstedt for references to authors just cited.
6. Osgood and Lucas: Transmission Experiments with the Virus of Poliomyelitis, J. Am. Med. Ass., 1911, LVI, 495-497.
7. Kling, Pettersson and Wernstedt: Investigations on Epidemic Infantile Paralysis. Report from the State Medical Institute of Sweden to the XV Int. Cong. on Hygiene and Demography, Washington, 1912. Stockholm.
8. Flexner, Clarke and Frazier, 1913: Epidemic Poliomyelitis, 14th note; Passive Human Carriers of the Virus of Poliomyelitis, J. Am. Med. Ass., 1913, LX, 201.
9. Flexner and Lewis, 1909: The Transmission of Epidemic Poliomyelitis to Monkeys, J. Am. Med. Ass., LIII, 1913.
10. The correspondence in the symptoms shown by these children is most interesting. Harry A, Billy C and Jack C were each suddenly taken ill with high fever, vomiting, pain in the head, and in the back of the neck, hyperæsthesia and were at times irrational. All escaped paralysis. Their illnesses, which lasted from five to six days, were so similar that the description of one serves for the other two. No other cause for their illness could be found, dietetic or otherwise. The spinal fluid was taken in only one case (Jack C), and in that one case it showed the characteristic changes found in poliomyelitis.

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Turning now to the B children, the illnesses of Dorothy, Charlie and Bobby were absolutely identical up to the third day. The onsets were violent, timed to the half hour, marked by intense headache, high fever, extreme restlessness, hyperæsthesia and increased tendon reflexes. After the initial stage the improvement was rapid. On the second and third days Bobby B went out to play. Dorothy and Charlie would have done so at the same period had they been allowed. The only difference in the illnesses of the three children was that Bobby B's symptoms started up again on the third day, whereas those of Dorothy B and Charlie B ceased altogether. No cause for their illnesses other than poliomyelitis could be discovered. Bobby B died of the ascending type of paralysis (necropsy). No wonder that Mr. B remarked, when his fourth child was taken ill: "I don't know what the matter with the children is, but I am sure that they all have the same thing."

11. ROSENAU, M. J., AND BRUES, C. T.: Some Experimental Observations Upon Monkeys Concerning the Transmission of Poliomyelitis through the Agency of Stomoxys Calcitrans., Tr. XVth International Congress on Hygiene and Demography, 1912, 1, 616.
12. HOWARD, C. W., AND CLARK, P. F.: Experiments on Insect Transmission of the Virus of Poliomyelitis. Jour. of Exp. Med., 1912, XVI, 850.
13. RICHARDSON, M. W.: The Rat and Infantile Paralysis; A Theory. Bost. Med. and Surg. Jour., 1916, CLXXV, 397.
14. The baby's food consisted of Walker-Gordon milk and lactose.
15. Although we had no evidence to show that the colored maid was the carrier of poliomyelitis, we could not help but regard her with suspicion, because, on the one hand, she lived at home (going to and coming from her work at the A's apartment) in a negro district of the city, and, on the other hand, came into intimate contact, not only with the A children, but with almost all the children who were affected. She left the employ of the A's on September 25, the day on which it became known that the B children had poliomyelitis. We visited her home on three different occasions and at the two places of employment which she had obtained after her departure from the A's,

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FIG. 1.—A map of the city. The black dots, squares and oblongs represent the location of cases of poliomyelitis in the city up to the outbreak of the disease in the X House. The location of the X House is designated by an X at upper part of the map.

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but were unable to find that she had been exposed to any case of poliomyelitis prior to Harry A's illness, or that any cases of the disease had developed among those with whom she came in contact after she left the A family, as might have happened had she been a carrier.

16. In estimating the above incubation periods, we are fully aware of the dangerous ground on which we tread, and wish it to be understood that we regard them only as probable.
17. PASTEUR, W.: An Epidemic of Infantile Paralysis Occurring in Children of the Same Family. Transactions of the Clinical Society of London, 1897, XXX, 143.
18. EMERSON, HAVEN: Personal communication, 1916.
19. REECE: Proc. Roy. Soc. Med. (Epid. Sec.), 1911-12, V, 59; Report of Med. Officer, Local Govt. Board.
20. We should not regard the positive globulin without the presence of alterations in the cellular content as having any special significance.
21. *Loc. cit.*
22. LEEGAARD, CHR.: Kliniske og Epidemioliske Undersögelser over der akuten Poliomyelit i Norge. Vidensk. Selsk. Skr. Christiania, 1909.
23. MÜLLER, EDWARD: Die spinale Kinderlahmüng—Eine klinische und epidemiologische Studie. Berlin, 1910.
24. *Loc. cit.*

APPENDIX.

We wish to put on record two experiments which were performed in reference to the mode of transmission of the virus of poliomyelitis.

Experimental attempt to demonstrate the virus of poliomyelitis in money. Through the Health Department, a considerable amount of paper and silver money was collected from persons in houses exposed to poliomyelitis. The money was collected in a large, clean, freshly boiled museum jar which was fitted with a tightly fitting ground glass cover. It was placed directly into the jar by the persons from whom it was collected. The money was shaken with a small amount of normal saline solution; the mixture filtered through a Berkefeld filter and the filtrate injected by Dr. G. W. McCoy, into a brain ventricle and the peritoneal cavity of a healthy Macacus rhesus monkey. Dr. McCoy reports that this monkey did not show any symptoms.

Experimental attempt (in association with Dr. Kenneth D. Blackfan) to demonstrate the virus of poliomyelitis in dirt. Previous to the fumigation of the apartment and just at the time of the removal of the children from

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the B apartment (September 25), to the poliomyelitis hospital, the room in which they had remained most of the time of their illnesses was carefully swept. The sweepings which contained dust, lint, hair, hairpins and a few fruit seeds were placed in a clean, freshly-boiled museum jar, fitted with a tight cover. The material was dry and small in amount.

On October 18, the sweepings were covered with a small amount of normal saline solution and left to soak over night in the laboratory. On the following day the mixture was shaken and filtered through a Berkefeld filter. Under ether anæsthesia, 2 c. c. of the filtrate were placed in the right lateral ventricle and 5 c. c. into the peritoneal cavity of a small female Macacus rhesus monkey No. 8. This monkey had been in the laboratory for about four years. She appeared healthy.

The monkey remained well for two days after the injection but then became ill and showed weakness in her left hind leg. On the third day her right hind leg was also weak and, when moving, she dragged her hind parts. The illness in every way appeared to be comparable to that observed in Monkey No. 1. She did not develop, however, any prolapse of the rectum. On the fourth day she appeared very ill, her respirations were rapid, 50 per minute.

While under observation at this time she fell, fracturing her skull.

At necropsy the internal organs appeared normal except for hyperplasia of the lymph nodes of the intestines, spleen, lungs, mesenteric and bronchial lymph glands. The lumbar and dorsal cord was hyperæmic and œdematous and there were small hæmorrhages in the gray matter of the anterior horns of this region of the cord. The brain and cervical cord appeared normal except for slight congestion and hæmorrhage—the latter could be readily referred to fracture of the base of the skull. Microscopical examination of the cord revealed, however, little more than that seen in the gross. There were numerous hæmorrhages into the gray matter of the lumbar and dorsal cord. Many of the nerve cells in this region stain deeply but there was no definite cellular infiltration. Six dorsal root ganglia were examined without revealing anything. Pieces of the lumbar cord of this monkey were taken aseptically and preserved in 50 per cent glycerine.

Dec. 2, 1916. A thick emulsion in physiological salt solution of the glycerinated cord of Monkey No. 8 injected into Monkey No. 9.

One cubic centimeter was placed in the right lateral ventricle and 6 c. c. into the peritoneal cavity.

December 12, 1916. A thick emulsion in physiological salt solution of another part of the glycerinated cord of Monkey No. 8 injected into Monkey No. 6 (Monkey No. 6 had been used 6 weeks previously, in Experiment I (d), but had remained perfectly well).

Two cubic centimeters of the emulsion were placed in the left lateral ventricle and 2 c. c. into the peritoneal cavity.

Both of these monkeys have remained well up to the time of writing, January 22, 1917.

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PAPILLOMA OF THE LARYNX.

REPORT OF A CASE TREATED WITH RADIUM, WITH RESULTANT CHRONIC DIFFUSE THYROIDITIS.

By WM. C. DUFFY, M. D.

(From the Department of Pathology of The Johns Hopkins University, Baltimore, Md.)

The well-known tendency of papilloma of the larynx, to recur together with the rareness of study of the effect of radium on normal tissues, makes the autopsy on this case of recurrent papilloma, in which marked changes occurred in the thyroid and neighboring soft parts, one of unusual interest and importance.

Literature.—In the literature, no autopsy was found on any similar case, and clinical reports are relatively infrequent. Those reported up to 1913 were reviewed in that year by Harris, whose paper includes 10 from the literature and adds six new cases. Collectively, the results are very encouraging. Individually, the cases are somewhat sparse in data concerning the ultimate result.

Epitomes of Harris' Cases.

Case 1.—A woman, aged 30, had had aphonia and attacks of choking cough from 1893 until 1898. Papillomata were removed on three occasions. The treatment included preliminary tracheotomy with laryngotomy, excision, and cauterization. In 1907, 20 mg. of radium had been applied for only a total of 20 minutes (on account of irritability of the throat). Two years later there was a recurrence. "At present she talks loudly and plainly. The attending laryngologist has once snipped off a little bit of growth, but he regards the case as practically cured." This according to Harris is the first case of papilloma of the larynx treated with radium.

Case 2.—An elderly woman had had operations for papillomata of the larynx extending over 47 years. In 1908, after radium treatment "a large part rapidly disappeared; up to the time of her death three years later there was no recurrence." (Cause of death not stated.)

Case 3.—In this instance the patient was a girl, aged 17. In 1910 shortly after the onset of hoarseness papillomata were excised but rapidly recurred and were again removed. In June, 1911, aphonia and stridor developed and after tracheotomy 100 mg. of radium bromide were drawn into the larynx and allowed to remain for 30 minutes. Three months later no trace of the growth could be seen and at the time of writing the cords appeared perfectly healthy without scarring and the voice was normal.

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Case 4.—A woman, aged 34, who had had hoarseness for several months, showed a discrete growth on the anterior commissure and left vocal cord. Radium was applied in 15 sittings which totalled nine hours. The mass entirely disappeared, but the duration of the cure is not stated.

Case 5.—A man of 40, with a husky voice for the 10 years previous, showed a mass on the anterior portion of the left cord and inflammation of the entire larynx. Radium was applied altogether for 14 hours and the growth disappeared. No statement as to the duration of the cure is made.

Case 6.—A woman, aged 43, had had complete aphonia for three years. Papillomata covered the walls of the larynx. One hundred milligrams of radium were applied for 35 minutes in March, 1913. At the end of eight weeks only a number of small tags remained. When seen on May 29, 1913, the larynx was entirely clear except for a small mass on the right arytenoid. The voice was strong.

Thus there is one patient (Case 3) perfectly well after two years. In the other cases there is either still a residuum or else the length of cure is not stated.

Epitomes of the Three Cases of Polyak as Cited by Harris.

Case 1.—A woman of 26, who had had several previous operations for papilloma of the larynx, was treated with 15 mg. of radium bromide applied through the mouth in 16 sittings which totalled over 17 hours. This was followed by a recurrence of the papilloma after one year. Radium was about to be reapplied at the time the case was reported.

Case 2.—A child of 9 years, with a history of laryngo-fissure, excision and repeated recurrence of the papillomata, was treated with radium which was applied through the external opening for 21 hours altogether. The amount of radium was not mentioned. The growth disappeared and a recurrence after four months in turn disappeared after the application of radium for eight and one-half hours in five sittings. There had been no recurrence at the time of the report.

Case 3.—In a man of 35, who had been treated for papilloma of the larynx for one and one-half years by various methods, radium was applied for 20 hours in 15 sittings. This resulted in an entire disappearance of the growth with only a residual thickening of the right vocal cord. No recurrence took place (length of time not stated.)

Harris also mentions the case of a patient referred to by Killian at the Third International Laryngo-Rhinological Congress as "cured," who suffered a relapse and later was cured (again) by the Roentgen rays. He has also noted three cases treated with radium by Mazzochi, but does not state the latter's results.

Certain points of similarity to the case to be considered call to mind the most historically important case ever recorded—that of the late

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Emperor of Germany, who in 1888 succumbed to an analogous affection. In 1886 he began to suffer from hoarseness, following a succession of obstinate colds, and a small growth was seen on the left vocal cord. This was destroyed as thoroughly as possible with the electric cautery, but returned and spread rapidly. Six months after the onset fragments were excised and submitted to Professor Virchow. They showed only a hard, warty growth with no evidence of malignancy. The tumor returned after one month's amelioration of the symptoms, and the electric cautery was again applied. Within three months there was an accentuation of the symptoms and an authoritative clinical diagnosis of cancer was made. Radical removal was refused. A little more than a year after the onset a tracheotomy became necessary for dyspnœa. Miscroscopic examination, at this time, of expectorated particles was made by Waldeyer, who pronounced the condition cancer. Four months later another examination, by Virchow, resulted in no proof in the latter's mind of the existence of cancer. A month later it was evident that perforation into the œsophagus had taken place. The post-mortem made on June 16, 1888, by Professor Virchow showed that the condition was one of cancer of the entire larynx and replacement by a large abscess cavity.

Case Report.

A colored male infant, aged 3 years at death, had been treated for about a year by repeated excision, cauterization, tracheotomy and radium, for papilloma of the larynx. At autopsy there was chronic diffuse thyroiditis, acute necrotizing laryngitis and tracheitis, tracheo-esophageal fistula and bronchopneumonia.

***Clinical History.*—W. W., aged 3 years at death (General No. 107703, Autopsy No. 4596), was first admitted to The Johns Hopkins Hospital November 21, 1913.**

The family history was negative.

The child had had "cholera infantum" for one month in his first summer. For two months previous to his first admission he had had "snuffles." At this time he was admitted with the complaint of the discovery four days before of a swelling under the jaw which appeared to the mother to have increased considerably in size during this short time. In the throat dispensary a report was made that there was nothing in the nose or throat to account for the condition. The mass in the neck began at the angle of the right jaw and extended under the jaw to the mid-line of the neck. The spleen was slightly enlarged and palpable. The neck was retracted somewhat. Lumbar puncture was negative; aspiration of the swelling in the neck also was negative, a small amount of serum obtained showed no growth on agar.

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The temperature remained at 103° F. for three days. A clinical diagnosis of acute cervical adenitis was made and he was discharged as improved.

On December 18, 1913, the child was brought to the dispensary with a history of paroxysmal coughing for a week. A diagnosis of pertussis was made.

The child was not seen again until February 17, 1916, when he was brought back and a history of difficult breathing was obtained. When frightened he would be unable to make a sound. At this time the diagnostic possibilities were recorded as tetany, papilloma of the larynx, and laryngitis.

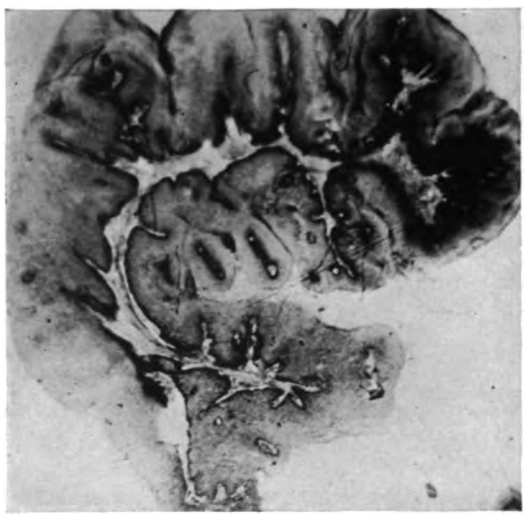

FIG. 1.—Very low magnification of a section through one of the papilloma masses removed at operation early in August, 1915. See text.

March 3, 1915.—A mass of adenoids was detected in the naso-pharynx and it was thought enlarged lymph glands were felt behind the posterior wall of the pharynx. The mother stated that the child had been very hoarse for about four months and that, while he occasionally "spoke," most of the time he "whispered." Several attacks had occurred during which he could not get his breath and his chest was retracted.

On March 9, 1916, the child was admitted to the hospital. The larynx was examined and the following note made: "Epiglottis seems quite normal. No true cords seen, but soft masses, larger on the left, fill the larynx. Very little space for air. These masses move with respiration and seem attached to the true cords." On March 27, 1915, 564 mg. of radium element were applied for six hours and forty minutes, one and one-half inches from the skin surface. A radium burn the size of a quarter appeared

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under the chin and on April 17, 1915, there was still considerable growth on each cord.

The skin burn healed, but by June 10, 1915, large polypi had developed on both false cords. The patient, however, was able to talk intelligibly, whereas before treatment he had been unable to speak.

On June 26, 1915, a tracheotomy was performed and the growth was then fulgurated.

On July 22, an attempt to apply radium intralaryngeally was not successful; the radium was in the larynx only a few minutes.

On Aug. 7, 1915, large masses of papilloma were removed from the aryteno-epiglottidean folds and from the ventricular bands. The true cords were not involved.

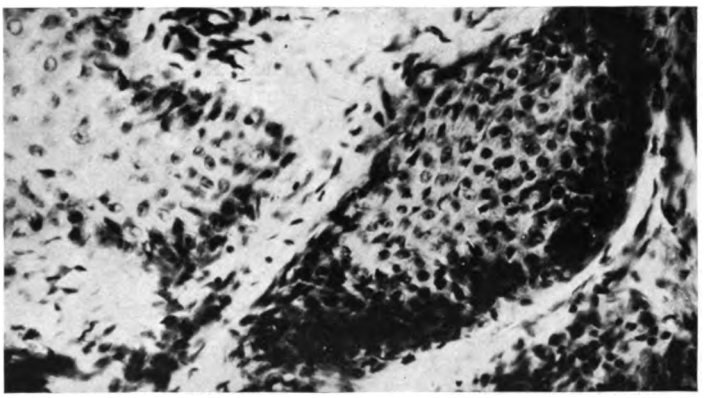

FIG. 2.—Somewhat higher magnification of the preceding structure. The field shown includes portions of two epithelial processes and fibrous stroma.

Microscopic Note on Tissue Removed Aug. 7, 1915.—The tissue was removed at a time when there had been no direct radium exposure but only an external application on March 27, over four mouths before. The section shows a pedunculated squamous-epithelial papilloma. The surface is smooth, but shows numerous convolutions and sulci. The epithelium rests on a narrow central core of connective tissue which contains blood-vessels showing no thickening. The epithelium has a well-defined basal zone composed of somewhat irregularly palisaded cylindrical cells. Toward the periphery the cells rapidly became larger and more cuboidal and show abundant inter-cellular spines. On the surface they are somewhat flattened but no definite keratinization is present. In the basal layers occasional mitotic figures could after some search be found; they were not numerous and were not found at all in the more external layers. The cells of the latter were strikingly large and pale with vesicular nuclei, both nucleus and cell being of a fairly constant cuboidal or oval outline. There was no tendency to formation of epithelial pearls.

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Section through a bit of the pedicle shows a continuation of the connective-tissue core of the papilloma with marked round-cell infiltration and occasional single cells or small groups of cells, which are similar in appearance to the type of cell of the tumor proper. These, however, must be admitted to be a negligible evidence of invasive tendency.

Diagnosis: Benign papilloma of the larynx.

On Aug. 25, and Sept. 10, 1915, the laryngeal growths were fulgurated and tracheotomy tubes were changed. The patient had complete aphonia. On Sept. 28, 1915, when the larynx was found to be filled with grape-like masses of papilloma, 103 mg. radium element were introduced into the larynx in a soft rubber catheter and allowed to remain for 45 minutes. On October 30, radium treatment was attempted but failed; the catheter could not enter the larynx on account of large masses of papillomata. On November 5, 100 mg. of radium were introduced in a small catheter through the tracheotomy opening and left in the larynx for one and one-half hours. Similarly, on November 20, the radium was inserted and left for two hours. The papillomata appeared smaller, their color pale and greyish. On December 21, 1915, radium was again inserted ("with more ease than on previous occasions") and left in for an hour and fifty-five minutes. On Dec. 28, the patient had a coughing attack in which milk was expelled through the tracheotomy tube. Several attempts were made to pass a stomach tube but each time the tube entered the trachea. The patient was discharged on January 13, 1916, still coughing liquid through the tube.

On February 5, 1916, he was again admitted to the Harriet Lane Home. Since his discharge he had had a cold with almost constantly high fever.

On examination he appeared to be in considerable discomfort on account of obstructed respirations through a dirty tracheotomy tube from which a foul-smelling blood-stained muco-purulent material issued. There was dulness at the right apex and over the right back. The patient's condition continued bad. The temperature ranged from 102° to 104° F. Efforts at gavage showed that the tube entered the trachea instead of the esophagus. Exitus occurred on February 16, 1916.

Autopsy No. 4596.—The *body* is that of a small, emaciated, colored male infant, 82 cm. in length. In the mid-line of the neck anteriorly is an incision 2 cm. in length. Aside from the extreme emaciation there is nothing else remarkable about the exterior of the body.

Neck Organs.—The tongue, trachea, esophagus, tonsils and soft palate were taken out *en masse*. The tongue shows nothing remarkable. At the bifurcation of the trachea is seen a group of enlarged lymph glands measuring about 2 x 3.5 cm. Anteriorly, in front of the trachea and on the right side, may be seen three or more similar glands. These glands are rather soft and on section show nothing remarkable save that they are spongy and red, apparently owing to congestion. The trachea is opened from behind and similarly the esophagus and the larynx are exposed. The normal diaphragm between the trachea and the esophagus for a distance of 5 cm. below the lower level of the larynx has disappeared

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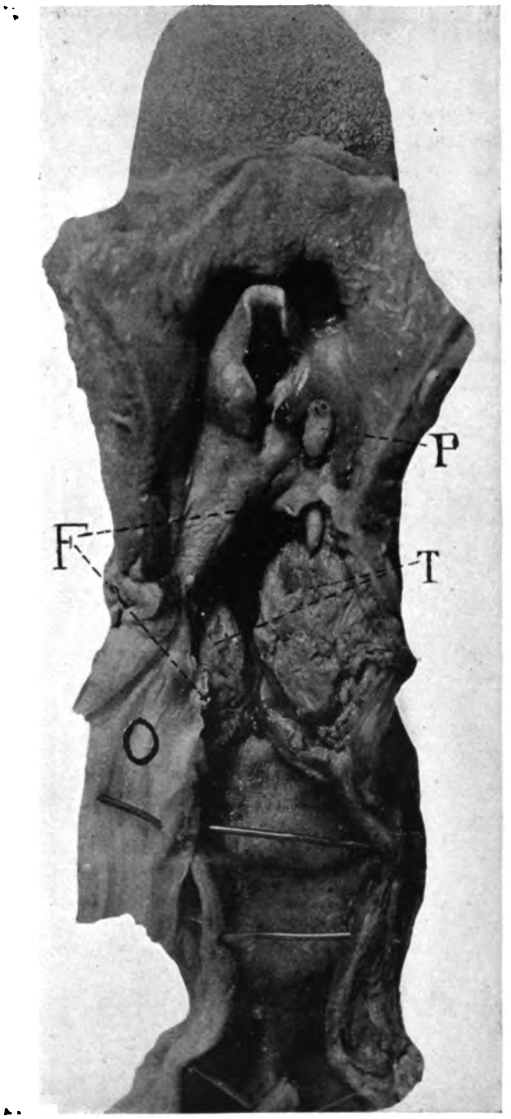

FIG. 3.—Posterior view. The borders of the tracheo-œsophageal fistula are seen at *F*. *O* = œsophagus. *T* = lateral lobes of thyroid encroaching on the lumen of the trachea. *P* = papilloma just below which is the lighter colored area of the inflammatory zone. The uvula and surrounding parts of the larynx look slightly thickened. Note the shaggy necrotic pseudo-membrane covering the thyroid.

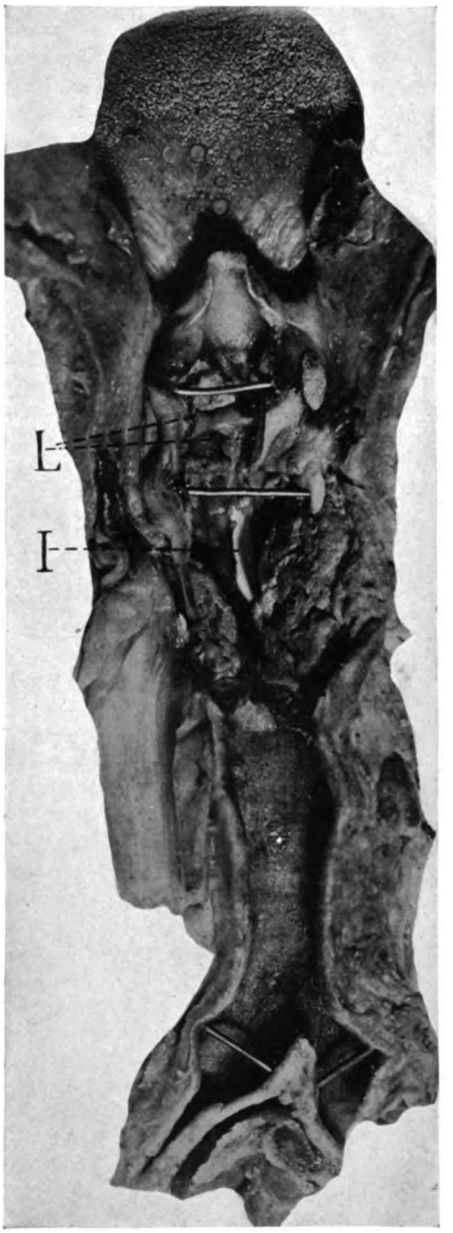

FIG. 4.—The larynx (*L*) has been opened from behind. The destruction of its soft part is shown. *I* = tracheotomy incision. A mass of glands is present at the bifurcation of the trachea.

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so that a fistula exists between the esophagus and the trachea. The edges of the esophagus in this area are seen as frayed-out bits of tissue which are yellowish grey in color. Looking into the larynx from behind one sees the exposed surface of the arytenoid cartilage on the right. The true and false cords are both destroyed. No trace of either remains. The firm white wart-like process in the right recessus pyriformis appears to be the only residuum of neoplastic character. Looking forward in the mid-line may be seen the tracheotomy opening which was made between the two lobes of the thyroid gland. The necrotic inflammatory process, which has been referred to, extends downward to below the point where the esophagus and the trachea part and its advancing edge is rather sharply defined. In an upward direction the inflammatory process extends into the cavity of the larynx itself involving practically all its internal structures as far upward as the base of the epiglottis and laterally into the laryngeal fossæ. The tonsils are small; the uvula is thickened.

Thyroid.—There seems to be a definite constriction of the tracheal lumen by the lateral lobes of the thyroid which, on the right and over a less extensive but similar region on the left, are seen projecting into the lumen of the trachea. The internal surface of the thyroid and trachea in this zone is covered with a grey necrotic-looking pseudo-membrane.

On gross examination the thyroid is apparently not enlarged. It is of a firm, very dense consistence. On section it cuts with greatly increased resistance more like solid fibrous tissue than thyroid; the cut surface is a grey yellowish color with no grossly visible translucent areas of colloid. Here and there one discerns bands of whiter fibrous tissue. Sections made horizontally through either lateral lobe show that the capsule of the gland blends imperceptibly with the surrounding fibrous tissue and muscle, its location being indicated only by minute spaces, just visible at close range, which on miscroscopic examination proved to be the capsular vessels. It is of note that the thyroid was not recognized as such at autopsy. So dense a consistence and such an altered appearance did these masses, exposed through the wall of the trachea, present, that they did not suggest thyroid tissue at all. Following the discovery of the changes which had taken place in the thyroid after microscopic study had been begun, the entire gland was sacrificed, serial blocks made and sections cut.

It should be noted that there seemed to be a relatively small amount of lymphoid tissue in the thymus for one of such an age.

The remainder of the gross description is not of interest save that an extensive bronchopneumonia was present.

Microscopic Study.

Broadly, the points of interest are the study of the neoplastic remains, and the changes which have taken place in otherwise normal tissue as a result of radiation or inflammation. The former will be considered first.

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Section Through the Papilloma Which was Present in the Pyriform Fossa.—There has probably been some shrinkage. At present the papilloma, as seen in the section, measures 3.5 mm. in length x 0.5 mm. in height. The zone of necrotizing inflammation does not reach the papilloma, stopping a few millimeters "below" it at one side of the section. The papilloma shows no necrosis; its cells everywhere take the stain well. At its upper end the transition from mucous membrane to tumor is gradual, *the epithelium becoming progressively thicker.* At the upper extremity the tumor projects over the surface of mucous membrane for a distance of 1.5 mm. The papilloma is composed of

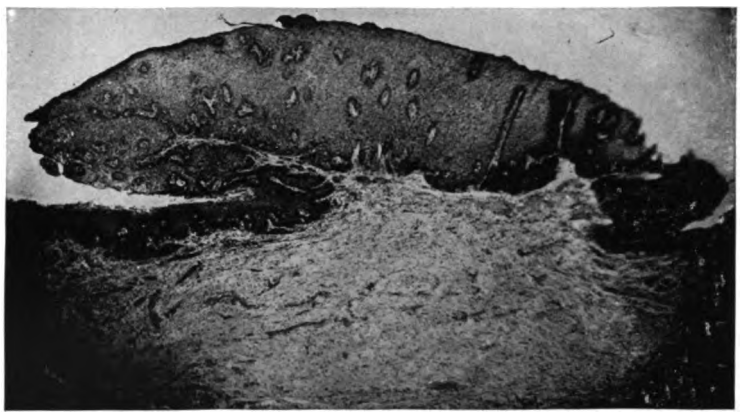

Fig. 5.—Section through the papillomatous process shown at *P* in Fig. 3. The mucous membrane is thickened and slightly irregular to the left of the pedicle.

layers of epithelial cells which correspond to the different layers of the normal mucosa, but the cells of the individual strata are considerably increased in size and numbers. There are no epithelial pearls. In the papilloma are seen cross-sections of blood-vessels, about each of which are one or two layers of basal-celled epithelium which shades off into the surrounding, more lightly staining cells. A few mitotic figures are found in these circumvascular basal layers. The basal layer of the papilloma is well demarcated from the underlying stroma. Its cells are perhaps not so regularly arranged as in the normal mucous membrane, and one finds an occasional mitosis. In one place is a small down-dipping of epithelium, the cells of which are fairly regular, however. It is notable that one finds more evidence of cellular activity

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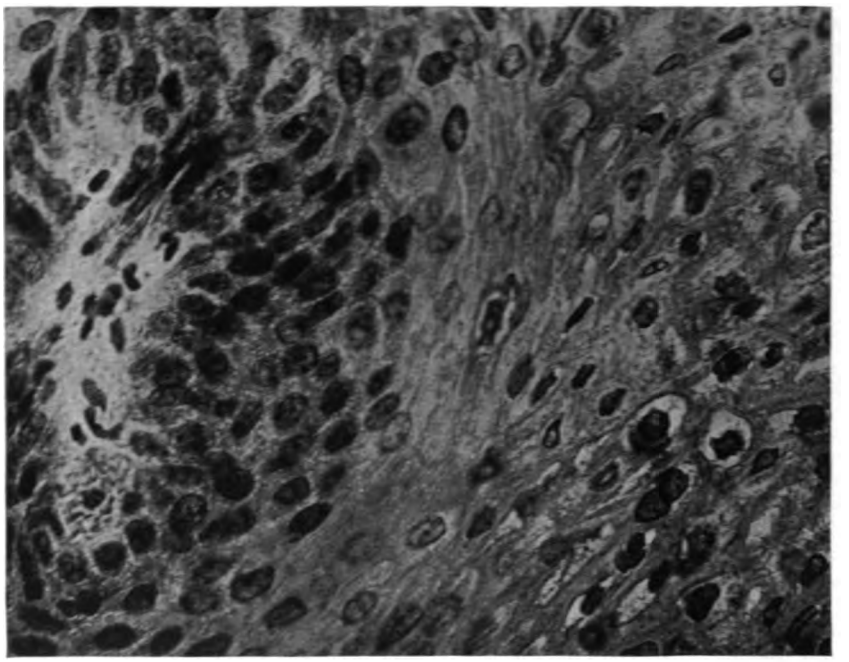

FIG. 6.—Higher magnification through the structure shown in Fig. 5, including one of the basal-celled areas at the left. To the right the vesicular type of cell which was seen in Fig. 2 is well shown. No mitoses.

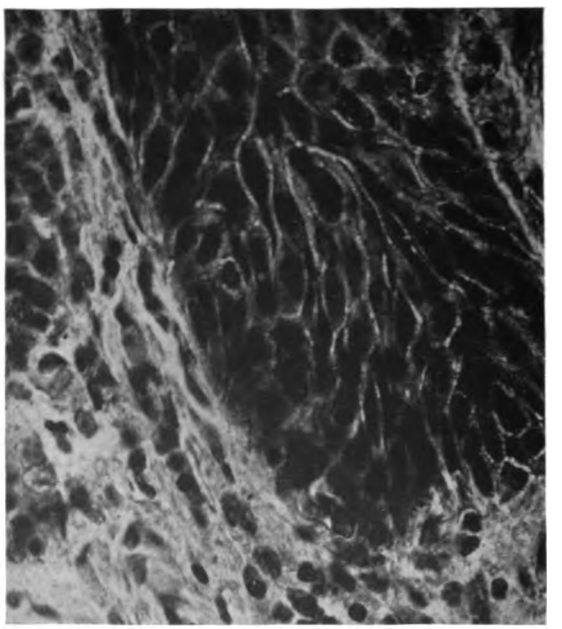

FIG. 7.—Section through one of the processes to the left of the papilloma shown in Fig. 5. Heavily chromatinized cells may be seen.

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in the basal layers of the mucous membrane to either side of the papilloma, a probable indication of diffuseness or spreading of the process. Here the epithelium is about three times its normal thickness; the small mucosa blood-vessels are increased in numbers and the epithelial processes extend into the stroma for short distances. The lowest layers of these processes have lost their regularity; the demarcation between epithelial process and stroma is vague, and in a few

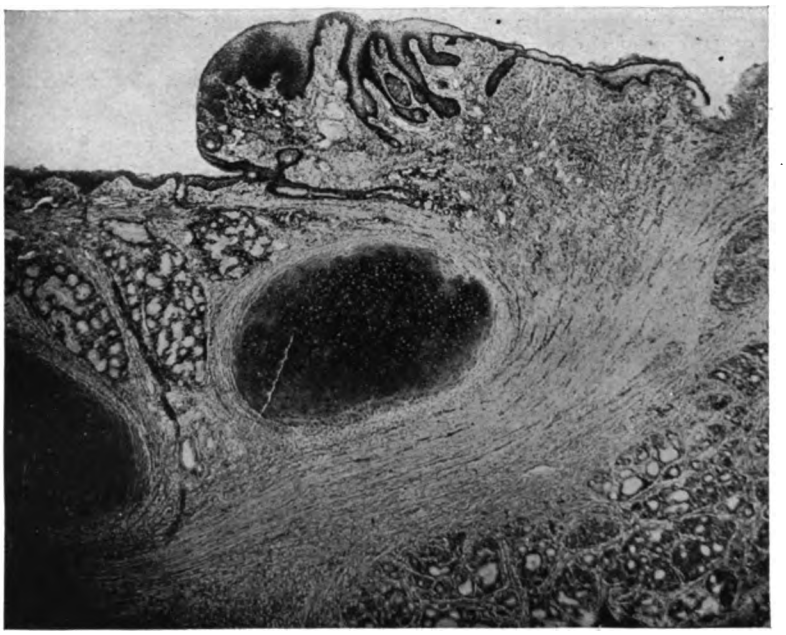

FIG. 8.—Vertical transection through first two rings of trachea. On the surface is shown hypertrophic squamous epithelium which is becoming columnar below the first ring. The necrotic surface zone is shown, below which level in the thyroid the fibrosis is evident. Mucous glands between the two rings.

instances one would be at a loss to designate an appropriate place for the "basement membrane," since numbers of small aggregations of epithelial cells lie in the stroma. These do not resemble small processes cut at varying angles, but their lack of arrangement, together with the indefinite basal layer of the adjacent mucous membrane, gives the impression of their having grown through into the connective-tissue stroma. Just at this point there are a number of small blood-vessels

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seen in longitudinal section entering the mucosa from below and passing through the groups of cells just mentioned. In these latter groups no mitoses are found. Below the epithelium, throughout this section, may be seen a varying amount of round-cell infiltration, including a few plasma cells and a number of lymphocytes. In the stroma, in front of the advancing edge of necrosis above referred to, may be seen a more striking picture. Large numbers of plasma cells and eosinophiles are seen. Of the latter, a few are polymorphs, but many are mononuclear. (No striking number of eosinophilic leucocytes was found in any of the other sections.)

Section through the lymph glands at the bifurcation of the trachea shows only an acute lymphadenitis.

Sections Through the Thyroid and Cross-Sections of the Upper Three Tracheal Rings.—The necrotizing process involves the mucous membrane downward for a distance of about two-thirds the length of the section. Just below this point one reaches the level of the first ring of the trachea, and here one sees a moderate degree of epithelial hyperplasia. Below this level one sees metaplasia of the epithelium from squamous to columnar. Normally, the squamous epithelium gives way to columnar just below the vocal cords. Hence this hyperplasia and metaplasia are remarkable. In addition to its presence at such a low level, the squamous epithelium in this block shows moderate hypertrophy, well shown in one of the photomicrographs. Under a higher magnification occasional nuclei suggesting mitoses are seen.

Sections through the left side of the entrance to the larynx show some epithelial hyperplasia. In a few instances cells may be seen extending into the stroma from the hypertrophic processes.

Microscopic Study of the Thyroid and Cervical Tissues.—The thyroid gland and surrounding tissue were cut in serial blocks, after fixation, embedded in celloidin and paraffin. Sections were stained with hematoxylin and eosin and by the van Gieson method. Paraffin sections were stained with methylene blue and eosin. Examination of sections shows a remarkable *universal chronic diffuse thyroiditis.* This consists principally of a widespread fibrosis associated with changes in the parenchymal epithelium. In some areas there is a marked hyaline change in the fibrous tissue, whereas other areas are present in which the connective-tissue cells are less rich in fibrillar substance, are spindle-shaped and contain numerous nuclei showing a

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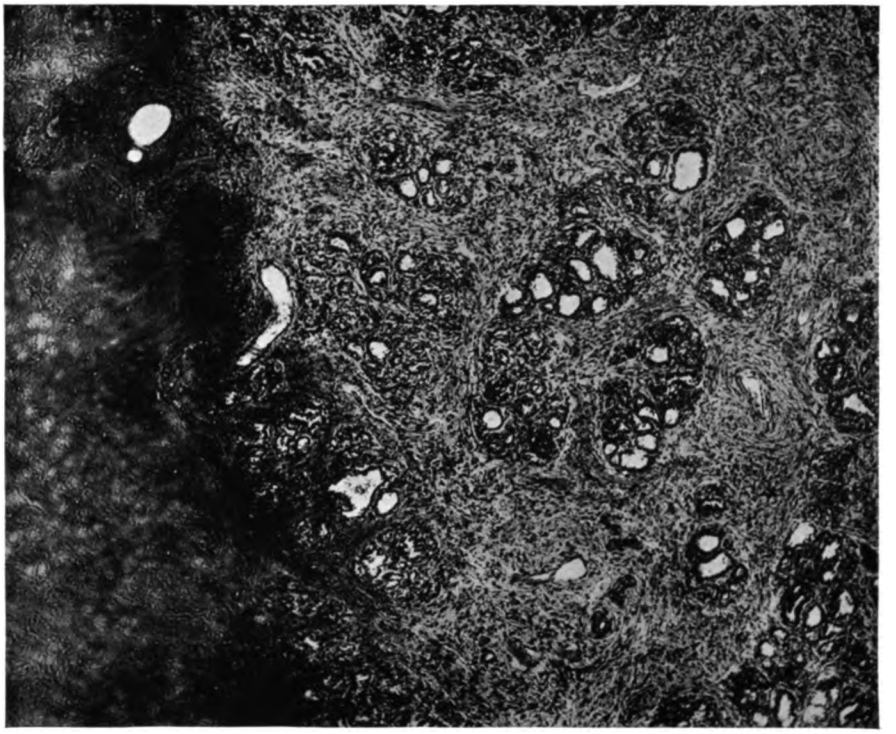

FIG. 9.—Section through thyroid and the necrotizing inflammatory process which covered the interior of the larynx and surrounding surfaces. The darker zone marks the advancing edge of the acute process. The diffuse fibrosis of the thyroid with diminution in number of acini is striking. Practically no colloid in this area.

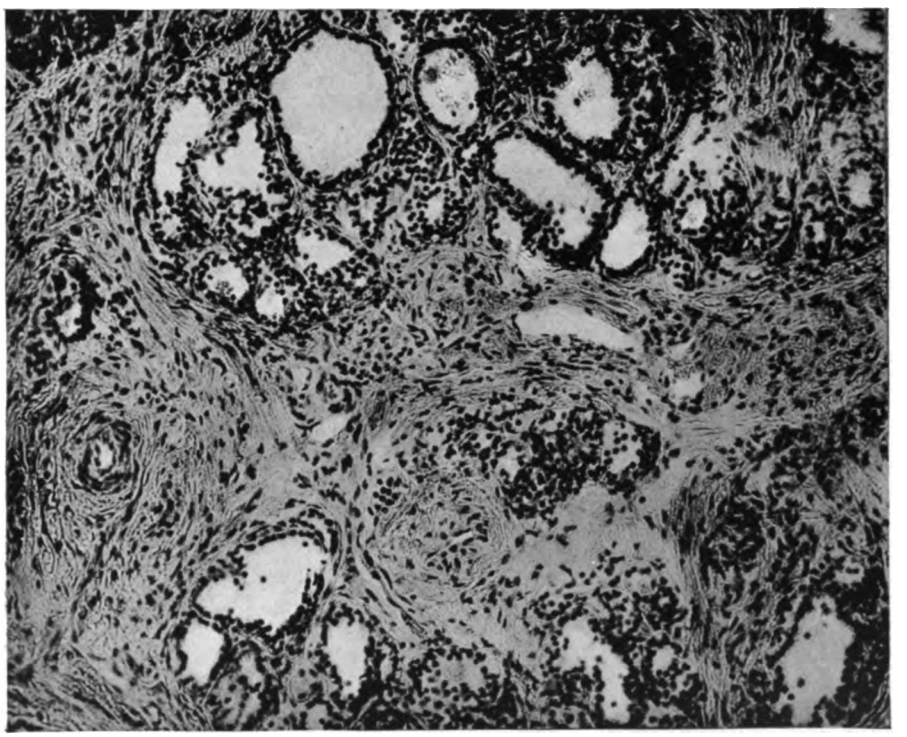

FIG. 10.—A higher magnification of the thyroid. The relative variety of acini, absence of colloid, and tremendous fibrosis without acute cellular reaction, are shown. The epithelium is flat or low cuboid.

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fairly rich chromatin content. One nucleus was seen with its chromatin collected into from 12 to 15 densely staining spheres. These areas of young connective tissue are less extensive than those of the adult tissue which predominates throughout the thyroid gland, infiltrates the capsule of the latter, firmly encircling the capsular vessels, and extends into the neighboring soft parts with a marked involvement of the adjacent muscles, many of which are largely replaced by fibrous tissue. (Care was used in discriminating tendons from fibrosis.) The carotid artery is involved in this mass, but itself shows no marked changes. One of the parathyroids at the left lower pole was sectioned and shows

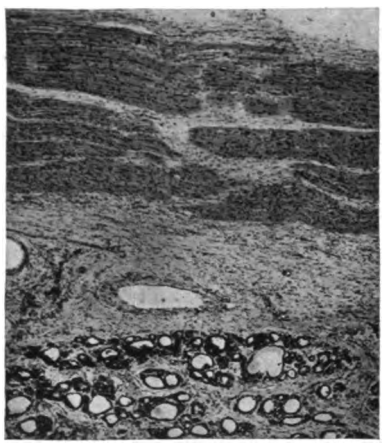

FIG. 11. — Low magnification through periphery of left lobe. Beyond the thyroid is the greatly thickened capsule. The fibrosis extends into adjacent muscle.

no definite fibrosis in its parenchyma or other change save that it lies in a more dense tissue than normally. Several nerves seen in the sections lie in a dense fibrous tissue.

The thyroid acini vary in size, but mostly tend to be quite small, of a type and size consistent with the age of the patient. Comparatively few acini have the average size found in glands of normal adults. The epithelial lining is mostly cuboidal or flat; no definite hypertrophy is found anywhere; no columnar or even low columnar epithelium. There is a scant amount of colloid present, which seems in some sections more abundant on the side of the gland away from the necrotizing process.

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In many acini there is a faintly staining, finely granular material which is evidently a much attenuated colloid. Evidence of epithelial degeneration is not wanting. One sees in acini of various sizes small groups of the lining epithelium which stain poorly—both nucleus and cytoplasm. In the thick stroma may be seen occasional groups of epithelial cells which are possibly residuals of destroyed acini. In agreement with this supposition one sees several instances of actual growth into acini of processes of fibrous tissue—certainly a rare phenomenon. Various phases of it may be seen, from single involutions to the protrusion into a vesicle of a bared tuft of connective tissue. Frequently

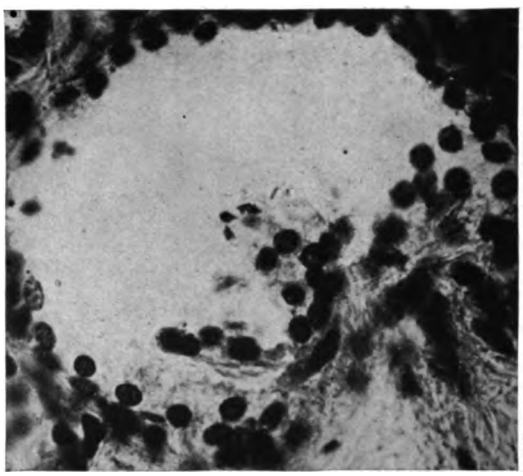

Fig. 12.—A tuft of fibrous tissue which has broken into an acinus.

the epithelium at the point of invasion is of feeble staining ability, but not always. The acini showing this invasion are always devoid of or show only the faintest trace of colloid.

Frequently in the acini are found groups of exfoliated epithelial cells. These cells tend to have a more eosinophilic cytoplasm than the lining cells. In many acini fairly numerous red blood cells occur. This has been noted by Welch as occurring rather commonly in the normal gland and is of no significance here.

There is no apparent difference in the degree of fibrosis between the portion of the gland which extends below the level of the tracheal necrosis and elsewhere.

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Bordering the tracheal lumen is a well-defined band of necrotic tissue 2 mm. thick. At its advancing edge it has extended into the thyroid gland. In the vicinity of this necrotic zone there is marked fresh granulation-tissue reaction with many young capillaries. The small vessels throughout the thyroid show marked thickening and endarteritis. This latter change may be seen well in older vessels near the zone of acute inflammation, where one was found of such a size and appearance that it simulated slightly a healed miliary tubercle. There was no

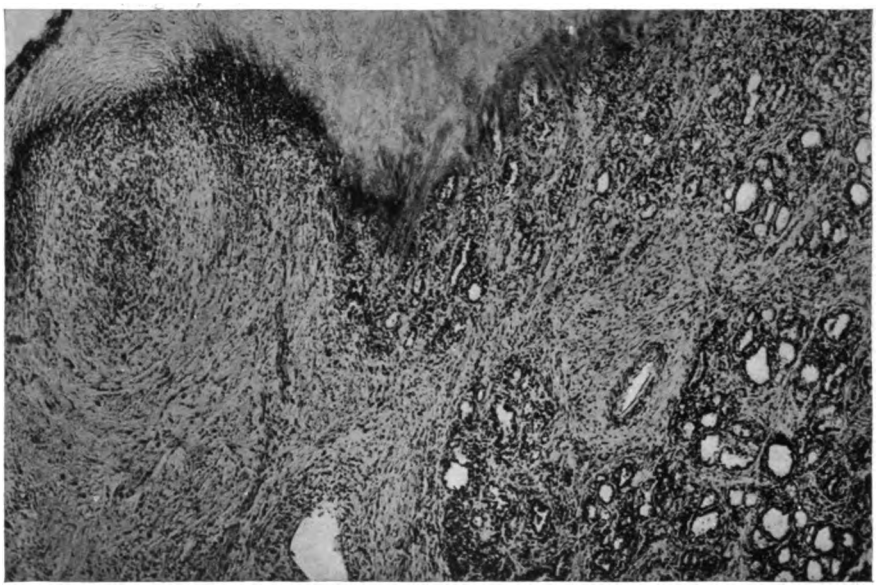

Fig. 13.—Section through necrotic zone and border of thyroid; an obliterated vessel is shown at the left. One of the capsular veins may be seen lying in a mass of fibrous tissue.

necrosis, and one could detect a minute lumen with a few red blood cells. In the acute necrotic zone every trace of normal structure is destroyed. At the advancing edge there is a marked cellular reaction, consisting of polymorphs and mononuclears, many of which are plasma cells.

Sections Through the Skin Edge of the Tracheotomy Wound, Subcutaneous Tissues, Muscles and One of the Lateral Lobes of the Thyroid.—The edge of the incision throughout the different strata shows a necrotic zone. The cellular reaction here, however, is not intense.

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There is a marked thickening of the subcutaneous tissue. Sections through the necrotizing membrane, stained with methylene blue, show numerous spirilla and fusiform bacilli in the necrotic zone.

It seems of considerable interest that the changes described in the thyroid and surrounding tissues of this case in which a known etiological factor was present correspond exactly with the pathology of the rare condition which was first observed by Riedel[10] in 1883. This is a "strumitis," or "thyroiditis" (sometimes the gland not being enlarged) which involves diffusely, in the great majority of cases, all lobes of the thyroid—a chronic inflammation of unknown etiology associated with a degeneration of the parenchyma and a fibrosis of the gland, in part or as a whole, together with the surrounding soft parts. The cases which have been reported are most remarkable clinically, because in most of them the indurated mass consisting of gland, capsule, muscles, etc., simulated perfectly a malignant thyroid. Thus in Riedel's first case: A man, aged 42, for half a year had noticed an enlargement of the thyroid and increasing respiratory difficulty. On examination there was not a very large, but extraordinarily hard, immovable, bilateral tumor of the thyroid. The diagnosis of a malignant struma was made. At operation it was seen that the tumor on both sides had grown fast to the carotid artery and internal jugular vein. A small piece of the internal jugular was resected, together with a walnut-sized piece of the thyroid, and the wound closed, the condition being considered inoperable. Microscopic examination showed no trace of malignancy or tuberculosis (syphilis was denied by the patient). The patient made a complete recovery, his respiratory difficulty disappeared, he was delighted with his condition and returned to work in the course of a year. Microscopic examination showed only a chronic inflammatory condition. Riedel did not publish this case for 12 years, until, in the course of over 300 operations for goitre, he came upon a second of its kind: A woman, 23 years old, for a year had noticed that her neck was becoming thicker; for more than two months the goitre had grown quite rapidly and become strikingly firm and fixed. Respiratory difficulty would ensue on exertion with slight palpitation and finally dysphagia appeared. On examination a goitre the size of a hen's egg on the right and the size of a small apple on the left was found; it was not definitely movable with the trachea. She had an outspoken goitrous voice. The pulse was 90. At operation (January 8, 1896) such an enormous involvement of the large vessels and N. recurrens was present

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that removal of the tumor was deemed impossible; only a small piece was taken out. Microscopic examination showed only an inflammatory tissue. After operation her symptoms cleared up quickly. Death occurred suddenly three months after the operation, probably from embolus; there was no autopsy. A third case reported by Riedel is very interesting, in that the progress of events was followed for 14 years, at the end of which time the patient was still well and was at work. This case is one of the few in the literature in which the growth was unilateral. Its onset was in May, 1896, with the discovery by the patient of a small hard tumor in the neck, which in the course of four weeks had involved all the right side of the neck and impinged on the median line. Meantime dyspnœa appeared. At operation extirpation was impossible on account of involvement of the neighboring muscles, vessels and nerves. A small extremely hard fragment was removed. The operation was then abandoned, it being clear that a strumitis and not a tumor was present. Following this operation (July, 1896) there was no relief of dyspnœa, crises of asphyxia occurred, and more or less cyanosis was usually present. At the second operation, in January, 1897, a piece of the isthmus, measuring 2 x 3 cm., was excised, and the trachea, which was encircled, was liberated. The asphyxial danger now disappeared, the dyspnœa gradually diminished and the mass retrogressed. When seen last in 1909 there was no trace of goitre. This case, as pointed out by Heineke,[8] disproves the one of Poncet[9] of malignant goitre and fibrous degeneration of the thyroid gland, which histologically was a typical Riedel's thyroiditis, but was called carcinoma because of positive serological tests.

A number of communications have appeared since Riedel's contribution, well reviewed by Heineke,[8] and by Delore and Alamartine.[8]

Clinically the condition is about twice as frequent in men as in women. Commonly it occurs in the third and fourth decades, but a case was described by Cordua in a 12-year-old girl and one by Walther in a 60-year-old man. Often a pre-existing colloid goitre is present. In most cases the onset is very gradual; usually many months pass during the hardening process. In the early course the fibrosis is well limited to the gland itself; later, it may extend along the large vessel sheaths as high as the mandible or more rarely to the base of the skull (Tailhefer[10]). In most cases the whole gland is symmetrically and equally involved. Very rarely the process is limited to one lobe (B. Ricard and Spaunans[10]). Rarely has any other thyroid abnor-

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mality been found in this disease, but Silatschek [11] found a cyst in a case of his and in one of Heineke's cases a small "goitre" nodule was present.

In spite of the evident attrition of glandular tissue, deprivation symptoms have been observed only in two cases (Murray and Southam [8] and Case 1 of Heineke). Most of the patients recover after months or years, the induration retrogressing. The operative indication is to remove only sufficient tissue to relieve the pressure on the trachea; attempts at excision of large parts of the process are usually unhappy on account of intimate attachment to important structures—vessels and pleura. Histologically, there is a coarse, gross fibrosis throughout the gland which implicates also the surrounding soft parts, causing fixation of the thyroid.

The etiology of the condition is unknown, but it is supposed to be a chronic inflammation, probably bacterial. Cases have been reported, as Heineke points out, which have been incorrectly attributed to tuberculosis and syphilis. Küttner,[6] however, described a case with gummata in which the clinical course was similar to that of Riedel's thyroiditis.

As to treatment, Delore and Alamartine attribute to the X-rays an almost specific action. Murray and Southam consider this difficult to understand, since in exophthalmic goitre the rays are used to stimulate fibrosis. Operation is indicated when there is compression of the trachea, but only enough thyroid tissue should be excised (usually from the isthmus) to free the trachea. When deprivation symptoms have appeared, they have come on after operative procedures.

In reference to the difficulty attached to discriminating the reaction observed in radiated tissue from that which may result from an ordinary necrotizing inflammatory process, a case reported by Julius Broeckaert [3] is of interest. This case is recorded in a paper captioned "A Contribution to the Study of Spontaneous Healing in Undoubted Malignant Larynx Tumors." Grossly, the vocal cords, which early in the clinical course had shown involvement, were free from growth, but the epiglottis and the aryteno-epiglottidean folds were reduced to scarcely recognizable structures (this is well shown in an illustration). Here and there at the level of the upper laryngeal orifice, and particularly toward the base of the tongue, were found papillomatous tumor masses (1 or more centimeters in diameter). Microscopically, *the primary larynx tumor showed the presence of numerous irregular masses of connective tissue in the interior of which were enclosed*

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atypical strands and clumps of carcinoma cells. This so-called spontaneous healing is attributed by Broeckaert to a necrotizing inflammation occurring in an erysipelous laryngitis. The lungs showed numerous large metastatic masses. There is no record of microscopic examination of the thyroid.

Summary.

The widespread chronic diffuse thyroiditis which was found at autopsy in this case of papilloma of the larynx which had been treated with radium is particularly interesting. This overgrowth of connective tissue had encircled the acini, causing involutions and actual growth into acini of tufts of fibrous tissue. The fibrosis had spread through the gland capsule and involved the surrounding soft parts. These changes are essentially similar to the pathological aspects of the disease which Riedel described in 1896. In view of the adult character of the connective tissue throughout the greater part of the gland, some degree of compression of the trachea might be expected to have been present during life. Any symptoms of this, however, would have been obviated by the tracheotomy tube, which was constantly worn from before the time direct applications of radium were begun.

In addition to the chronic diffuse thyroiditis there was a superimposed acute necrotizing laryngitis and tracheitis, which had practically destroyed the soft parts of the interior of the larynx and had caused a tracheo-œsophageal fistula. This process is attributed to an excessive action of the radium rather than to any possible discrepancy in the size of the tracheotomy tube. The bacterial flora is apparently a secondary invasive phenomenon.

A small mass of papillomatous tissue was still present outside the larynx proper. It is of peculiar interest that this is one of the few instances in which by virtue of its location a definitely benign new growth is still frequently of malignant significance. That such growths may undergo malignant change is a mooted point, but there seems to be little doubt that such can take place.

Concerning the mechanism of the thyroid changes, it would be interesting if the sequence of events could be determined. Is the endarteritis that is present the prime factor in the process, which by impairing the nutrition of the gland causes a replacement fibrosis, or do the gamma-rays exert primarily a destructive action on the acinar epithelium? One can say that there seems to be scarcely enough wide-

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spread evidence of epithelial necrosis to warrant the latter view, and that in some way the growth of connective tissue appears to be closely linked with the destruction of gland epithelium. Evidence of this is supplied by the actual growth into acini of connective tissue. Whatever the sequence of events in this picture, it seems clear that a marked stimulus to the growth of connective tissue has been active. This view is in accord with the experimental observations of Exner, cited by J. C. Beck,[1] who in observing the action of radium on subcutaneous cancer found that development of connective tissue was the most active and earliest change and preceded destruction of the cancer cells. This reaction appears to differ only in its widespread character from that of an ordinary inflammation.

In conclusion, I wish to express my thanks to Dr. Winternitz for the material and facilities and many helpful suggestions, to Dr. John Howland and Dr. W. S. Halsted for the privilege of reporting the clinical side, to Dr. Admont Clark for some of the photographs, and to Mr. Edward P. Walker for the voluntary rendering of his excellent technical services in making the microscopic preparations.

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ANALYSIS OF AUTOPSY RECORDS.

The analysis of autopsy records which was begun two years ago with the co-operation of the Prudential Life Insurance Company, through its statistician, Mr. F. L. Hoffman, has progressed.

In the fall of 1915, at a conference between a committee from the hospital and Mr. Hoffman, it was agreed that not only the autopsy protocols but also the clinical histories would have to be reviewed in order to standardize the clinical and anatomical diagnoses.

A fund for the purpose, contributed to by both The Johns Hopkins Hospital and the Prudential Life Insurance Company, has made this work possible.

It is hoped that the volume to include the first 5000 autopsies will be completed during 1917.

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AUTOPSY STATISTICS.

CITY HOSPITALS BAY VIEW.

Table Showing Number of Autopsies Prior to 1913.

Year.	No. of Autopsies.
1908	84
1909	75
1910	88
1911	92
1912	72

Deaths and Percentage of Autopsies in Different Departments, 1913-16.

Service.	1913.		1914.		1915.		1916.	
	No. D.	% A.	No. D.	% A.	No. D.	% A.	No. D.	% A.
Medical	227	39	273	38	274	45	268	54.1
Phthisical	261	16	239	33	242	52.5	227	44.8
Surgical	55	44	77	43	69	39	60	50
Insane	88	3.4	86	20	67	30	42	42.8

Deaths and Autopsies 1913-16.

Year.	Deaths.	Autopsies.	% Autopsies.
1913	631	153	25.8
1914	675	228	33.8
1915	652	297	45.4
1916	597	294	49.1

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JOHNS HOPKINS HOSPITAL

Table Showing Percentage of Autopsies.

(This report is taken from records that are not entirely complete and is therefore subject to correction.)

	Med. service.		Surg. service.		Gyn. service.		Obst. service.		Ped. service.		Psy. service.		Urol. service.	
	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.
1911	122	74.5	136	33.0	25	36.0	10	40.0	.....	.....	.....	.....	.....	.....
1912	151	70.8	116	31.8	27	25.8	11	81.8	.....	.....	.....	.....	.....	.....
1913	108	85.1	107	34.5	22	36.3	4	17.5	92	57.6	5	100.0	.....	.....
1914	107	76.6	83	40.9	15	40.0	38	34.2	123	57.7	9	55.5	.....	.....
1915	96	70.8	96	65.6	21	52.3	27	70.3	138	59.4	13	61.5	.....	.....
1916	114	72.4	88	56.8	18	94.8	99	83.3	146	63.6	8	62.5	22	72.7

	Total number of deaths. 1911–1915.	Total number of autopsies. 1911–1915.	Per cent of autopsies. 1911–1915.
1911	293	149	50.8
1912	305	160	52.4
1913	338	203	60.0
1914	375	211	56.2
1915	392	251	64.0
1916	495	347 (+70=417)	70.1

Monthly Table Showing Percentage of Autopsies.—1916.

	Med. service.		Surg. service.		Gyn. service.		Obst. service.		Ped. service.		Psy. service.		Urol. service.		Total.	
	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.	No. of deaths.	Per cent of autopsies.
Jan...	7	100.0	9	55.5	1	100.0	10	80.0	7	42.8	1	0	3	66.6	38	68.4
Feb...	7	71.4	5	60.0	1	100.0	9	88.6	12	66.6	2	100.0	1	100.0	37	75.0
Mar..	5	60.0	11	81.8	2	100.0	6	100.0	13	69.2	1	100.0	4	75.0	42	78.5
Apr...	17	82.6	9	44.4	2	100.0	6	100.0	15	73.3	0	0	1	100.0	50	74.0
May..	12	83.4	6	50.0	2	100.0	10	80.0	13	53.5	0	0	1	100.0	44	70.4
June .	16	62.5	8	25.0	3	100.0	11	81.8	9	77.7	0	0	1	0	49	65.3
July..	7	85.7	10	70.0	1	100.0	6	100.0	23	43.4	1	0	2	50.0	50	64.0
Aug...	8	75.0	3	66.2	3	66.2	11	81.9	17	65.0	0	0	1	100.0	43	72.4
Sept..	5	100.0	6	33.3	0	0	6	83.3	12	58.3	1	0	0	0	30	66.6
Oct...	12	41.5	7	42.6	3	100.0	9	88.8	14	72.4	2	100.0	2	0	49	63.2
Nov...	7	85.6	8	62.5	0	0	7	56.8	4	50.0	0	0	3	100.0	29	68.1
Dec...	11	72.8	6	83.2	0	0	8	75.0	7	100.0	0	0	3	100.0	35	82.2

70 autopsies were performed on other than hospital cases, therefore the total number of autopsies performed during the year was 417.

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REPORT OF THE PHOTOGRAPHIC DEPARTMENT.

During the past year a feature that has added to the value of the autopsy records and to the interest of the weekly pathological conferences has been the work of the photographic department. This was started in the fall of 1915, in the hope of photographing all unusual gross and microscopical lesions as they occurred in the routine autopsies. It was felt that the protocols supplemented by such illustrations would convey the idea of a lesion more accurately than a verbal description alone, and furthermore, that the two weekly demonstrations would be more interesting and instructive if lantern slides could be shown of the gross and microscopical lesions which it is impossible to demonstrate in any other way.

At a considerable initial outlay a dark room was built and equipped. A camera was purchased, and suitable stands were constructed for taking pictures *in situ*, during the course of an autopsy or subsequently, of individual organs or parts. A Leitz microphotographic apparatus was set up in the dark room. Recently a special lantern-slide camera has been purchased. As the amount of work increased it became apparent that it would be impossible for a member of the staff to take even the most necessary pictures. A technician was therefore employed and trained in the special methods and problems of this line of work. With this equipment, then, and with a trained technician, the photographic recording of the important gross and microscopic findings has come to be an important integral part of the routine autopsies.

For a member of the staff to obtain a photograph, the procedure is as follows: As an autopsy is being conducted, the technician is available at any time to photograph any unusual finding which may appear. Thus it is often possible to show by a picture of the organs *in situ* a lesion or relation which it would otherwise be impossible to demonstrate subsequently. With the completion of the autopsy, again, any organ or part of an organ can be photographed either in its natural size or magnified. By magnification it is possible to show a small lesion, which it would be difficult to point out in any other way. When the microscopical sections have been obtained they can be brought to the dark room and all microscopical findings which may be of interest

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can be photographed. These pictures are then mounted and bound with the proper autopsy record. Lantern slides are made of any or all of the plates which may be interesting for demonstration. Thus, at a conference it is possible to show on the screen the evidence which it would otherwise be difficult or impossible to demonstrate.

These pictures have a further value. Each plate is filed away and the lesions are indexed and cross-indexed, so that the lantern slides and plates are quickly available for a lecture or demonstration at any time. Such a collection of photographs and lantern slides undoubtedly will increase in value proportionately with its size and completeness.

A field that has not been attempted is color photography. The expense and difficulty of the process has so far made it prohibitive, yet it is hoped that at some time it too will be available.

A. H. C.

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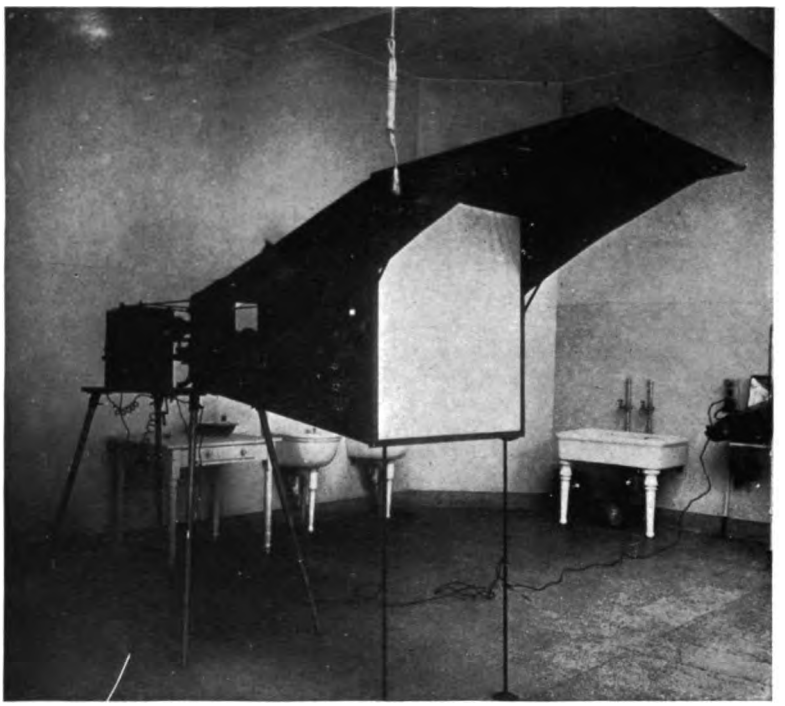
GENERAL IMPROVEMENTS.

Many changes have been made in the laboratory. Among the more important may be mentioned the installation of a modern morgue and refrigeration plant and an electric passenger elevator.

The autopsy ampitheatre has been equipped with a projection apparatus which is illustrated below. It was designed to project histological



preparations as well as lantern slides in a relatively undarkened room, and has proven very satisfactory. With it, it is not only possible to supplement the organ lesions with "situs" pictures, but the correlation of gross and histological changes, ever a problem where large groups are concerned, has been materially facilitated.

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DONATIONS.

Dr. Joseph H. Hewitt, who was graduated as a Doctor of Medicine of this University in 1906, and who died on January 26, 1916, bequeathed to the University his medical books, journals, and papers—the collection to be known as the "Departmental Library of the Department of Pathology of The Johns Hopkins Medical School." He added bank stock to the value of more than $5000, to enable the University to care for the library.

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